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A Temporary Phosphorus Tether/ Ring-Closing Metathesis Strategy to Functionalized 1,4-Diamines

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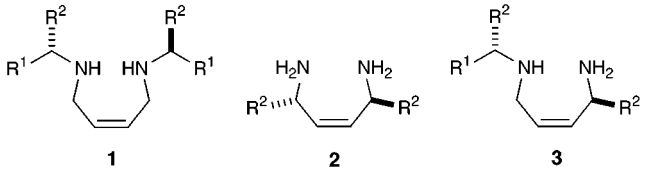
ABSTRACT



The synthesis of 1,4-diamines containing the (*Z*)-1,4-diaminobut-2-ene subunit via a temporary phosphorus tether/RCM strategy is described. We have developed a new method utilizing phosphorus nuclei as suitable temporary tethers for the coupling of nonracemic allylic amines. This approach allows for the generation of C_2-symmetric and unsymmetric 1,4-diamines 1–3, which may have considerable synthetic and biological utility. This represents the first synthetic pathway for the expedient coupling of two amines via a temporary tether approach.

Recently, nonracemic 1,4-diamines have served as key synthetic intermediates in the development of potent cyclic HIV protease inhibitors.[1] In addition, the potential of nonracemic 1,4-diamines to serve as biologically active agents[2] and asymmetric ligands[3] warrants continued efforts toward an efficient route to their synthesis. Previous methods reported for the generation of nonracemic 1,4-diamines include intermolecular pinacol coupling of α-amino aldehydes[4] and several chiral pool syntheses starting from tartrate[1b] or mannitol.[1d] Our interest in the ring-closing metathesis[5] (RCM) reaction on phosphorus templates[6] has led us to investigate a temporary phosphorus tether (*P*-tether)/ RCM strategy to the synthesis of 1,4-diamines.

Although temporary tethers[7] have been extensively utilized in organic synthesis,[8,9] examples of *P*-tethers have been

(1) (a) Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C.-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Vittanen, S.; *Science* **1994**, *263*, 380−384. (b) Patel, M.; Kaltenbach, R. F., III; Nugiel, D. A.; McHugh, R. J., Jr.; Jadhav, P. K.; Bacheler, L. T.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Garber, S.; Reid, C.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1077−1082. (c) De Lucca, G. V *J. Org. Chem.* **1998**, *63*, 4755−4766. (d) Hultén, J.; Bonham, N. M.; Nillroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Åqvist, J.; Classon, B.; Danielson, U. H.; Karlén, A.; Kvarnström, I.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 885−897.

(2) For examples of biologically active 1,4-diamines, see: (a) Rische, T.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 3917−3922 and refs 1−4 cited therein. (b) He, Z.; Nadkarni, D. V.; Sayre, L. M.; Greenaway, F. T. *Biochim. Biophys. Acta* **1995**, *1253*, 117−127. For the use of 1,4-diamines as dipeptide isosteres, see: (c) Baker, W. R.; Condon, S. L. *J. Org. Chem.* **1993**, *58*, 3277−3284.

(3) For examples of 1,4-diamines and their derivatives serving as ligands for metals, see: (a) Nivorozhkin, A. L.; Toftlund, H.; Jøergensen, P. L.; Nivorozhkin, L. E. *J. Chem. Soc., Dalton Trans.* **1996**, 1215−1221. (b) Fritsky, I. O.; Kozlowski, H.; Prisyazhnaya, E. V.; Karaczyn, A.; Kalibabchuk, V. A.; Glowiak, T. *J. Chem. Soc., Dalton Trans.* **1998**, 1535−1536. (c) Codina, G.; Caubet, A.; Lopez, C.; Moreno, V.; Molins, E. *Helv. Chim. Acta* **1999**, *82*, 1025−1037.

(4) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1992**, *57*, 28−32.

(5) For recent reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013−3043. (c) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211−240. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (e) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388.

(6) (a) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2000**, *2*, 1769−1772. (b) Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Synthesis* **2001**, 612−620 and references therein. (c) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3285−3288.

(7) For a comprehensive review on disposable tethers, see: Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289−2338.

(8) For a review on temporary silicon-tethered (*Si*-tethered) reactions, see: (a) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, *8*, 813−854. For additional references on *Si*-tethered reactions, see: (b) Ishikawa, T.; Kudo, T.; Shigemori, K.; Saito, S. *J. Am. Chem. Soc.* **2000**, *122*, 7633−7637. (c) Shuto, S.; Yahiro, Y.; Ichikawa, S.; Matsuda, A. *J.*

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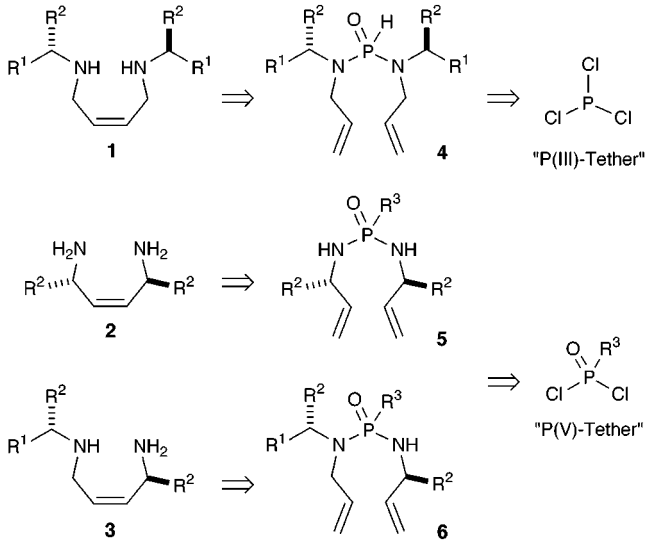
limited.[10] We now report a new strategy that allows for the rapid coupling of nonracemic allylic amines via a *P*-tether/RCM sequence[11,12] to derive *Z*-olefinic, C_2-symmetric 1,4-diamines **1** and **2** and unsymmetric, differentially substituted 1,4-diamines **3** (Scheme 1).[13]

Scheme 1



Our new method employs both intermediate phosphorous acid diamide **4** and phosphonamide species **5** and **6** containing P(III)- and P(V)-nuclei, respectively, as the central lynchpins for subsequent RCM (Scheme 1). The temporary cyclic *P*-tethers can be quantitatively hydrolyzed under mild acidic conditions to derive the title 1,4-diamines **1**−**3** containing the (*Z*)-1,4-diaminobut-2-ene subunit.

Our primary interest in C_2-symmetric 1,4-diamines **1** was rooted in our efforts to synthesize amino acid-derived 1,3,2-diazaphosphepine 2-oxides such as **A** and **B** (Figure 1).[6b,12c] These compounds and analogues thereof are similar in structure to DMP-323 and other potent HIV-1 protease inhibitors developed at DuPont Merck Laboratories.[1a−c] We determined that in order to generate phosphonamides such as **A** (R^3 = alkyl, aryl), containing exocyclic α-amino substitution, it is necessary to overcome steric congestion imposed by an α-branched secondary amine by first synthesizing the 1,4-diamine **1**,[14] coupling it with R^3PCl_2, and oxidizing at phosphorus.[12c]

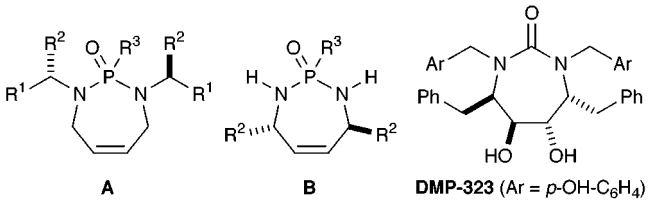
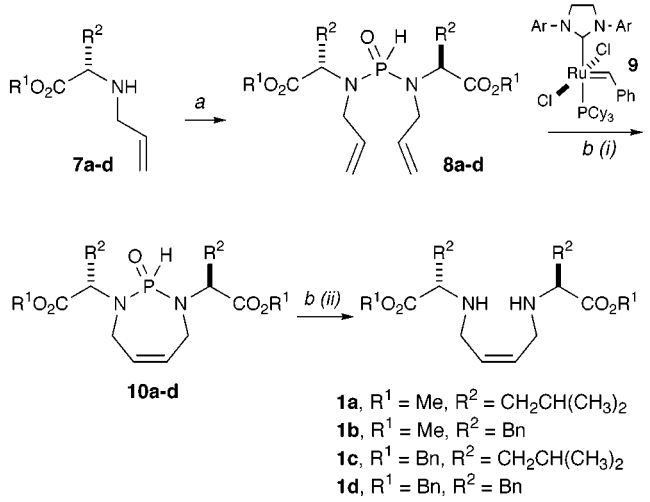


Figure 1.

Our initial strategy for the synthesis of **A** was to couple 2 equiv of an α-branched secondary allylic amine, such as **7**, with either a P(V)- or P(III)-dichloride, followed by RCM (Scheme 2). However, we found that, due to steric congestion imposed by **7**, the only phosphorus reagent which allowed the bis-coupling event to occur was phosphorus trichloride.[6b] Hydrolysis to **8**, followed by RCM with the first generation Grubbs catalyst,[15a,b] afforded 1,3,2-diazaphosphepine 2-oxide **10**.

Scheme 2[a]



[a] Reagents and conditions: (a) i. PCl_3, Et_3N, DMAP, CH_2Cl_2, reflux, ii. H_2O, 80−90%; (b) i. **9**, benzene, reflux, >95%, ii. methanolic HCl, rt, >95%.

Org. Chem. **2000**, *65*, 5547−5557. (d) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Aoe, K.; Okamura, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 6922−6931. (e) Rubinstenn, G.; Mallet J.-M.; Sinay, P. *Tetrahedron Lett.* **1998**, *39*, 3697−3700.

(9) For examples of metal-derived temporary tethers, see the following. Mg and Al tethers: (a) Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 6595−6596. Boron tethers: (b) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450−451. Al and Zn tethers: (c) Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.* **2000**, *2*, 1283−1286.

(10) For an example of a phosphoramidic P(V) temporary tether, see: Rubinstenn, G.; Esnault, J.; Mallet, J.-M.; Sinay, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1327−1336. To the best of our knowledge, there are no examples in the literature of utilizing P(III) as a temporary tether.

(11) For examples of silicon tethers utilized in the RCM reaction, see: (a) Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768−6769. (b) Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429−1432. (c) Gierasch, T. M.; Chytil, M.; Didiuk, M. T.; Park, J. Y.; Urban, J. J.; Nolan, S. P.; Verdine, G. L. *Org. Lett.* **2000**, *2*, 3999−4002. (d) Lobbel, M.; Koll, P. *Tetrahedron: Asymmetry* **2000**, *11*, 393−396.

(12) For other tethers utilized in the RCM reaction, see the following. Catechol tethers: (a) O'Leary, D. J.; Miller, S. J.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 1689−1690. Ketone tethers: (b) Rodriguez, J. R.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2000**, *2*, 3209−3212. Phthalamide tethers: (c) Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2000**, *65*, 7913−7918.

(13) For other methods of producing simple, unsaturated 1,4-diamines, see: (a) Radhakrishnan, U.; Al-Masum, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 1037−1040. (b) Courtois, G.; Desre, V.; Miginiac, L. *J. Organomet. Chem.* **1999**, *580*, 178−187. For a recent method of producing saturated 1,4-diamines, see ref 2a. (c) To the best of our knowledge, no general method exists for the preparation of nonracemic, differentially substituted 1,4-diamines.

(14) We have reported the synthesis of 1,4-diamine **1a** (Scheme 2) via a phthalamide tether/RCM/hydrolysis sequence. RCM yielded predominantly the *Z*-isomer (10:1 *Z*:*E*), see ref 12c.

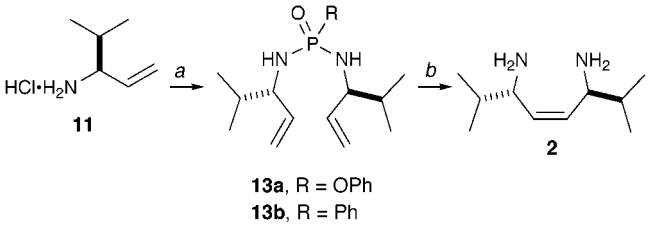
Due to the lability of the *P*−*N* bond to hydrolysis in cyclic species **10**,[16] we reasoned that we could employ the phosphorous acid diamide moiety as a P(III)-temporary tether in a one-pot RCM/hydrolysis procedure (Scheme 2). Optimization of the previously reported conditions[6b] provides acyclic RCM precursors **8** in 80−90% yield. Subsequent RCM utilizing the second generation Grubbs catalyst **9**[15c,17] in refluxing benzene, followed by facile cleavage[18] of the *P*-tether with methanolic HCl, results in quantitative yields of C_2-symmetric 1,4-diamine **1** with complete stereochemical and geometrical integrity. Furthermore, the RCM reaction is complete within several minutes, reaction scale is a nonissue, and the RCM/hydrolysis sequence is a single-pot event.

A number of other temporary tethers were also investigated,[19] including various metals[9a,c] (Cu, Fe, Mn, Mg, and Ni), as well as carbon (CO) and boron[9b] (BPh). Thus far, none have allowed this facile "di-amine" binding/metathesis sequence to occur. Our group previously reported an RCM strategy to generate cyclic sulfamides analogous to **10**;[20] however, the inability to effectively cleave the sulfamide linkage ($R_2NSO_2NR_2$) under mild conditions limits their utility in the production of 1,4-diamines such as **1**−**3**.

Moreover, while temporary silicon tethers[11] have been employed in the RCM reaction to access 1,4-diols, all of our attempts to prepare **1** from **7** utilizing silicon tethers ($SiPh_2$, $SiMe_2$, and $SiCl_2$) have been unsuccessful. We have found that not only does phosphorus appear to be the sole nucleus in which this 1,4-diamine chemistry is successful but the efficiency and ease of the sequence is extraordinary.

With this temporary bridging strategy in hand, we turned our attention to the synthesis of C_2-symmetric 1,4-diamine **2**, containing branching at the allylic positions (Scheme 3). Previously, we found that less sterically encumbering α-branched primary amines, such as L-valine-derived **11**,[21] readily couple twice with P(V)-dichloride **12a** to give **13a** in high yield.[6b] In addition, we and others[22] have shown that the reaction between phosphorus oxychloride ($POCl_3$) and 3 equiv of an α-branched primary amine, such as **11**, is facile to afford the corresponding phosphoramide.[23] Therefore, it

Scheme 3[a]

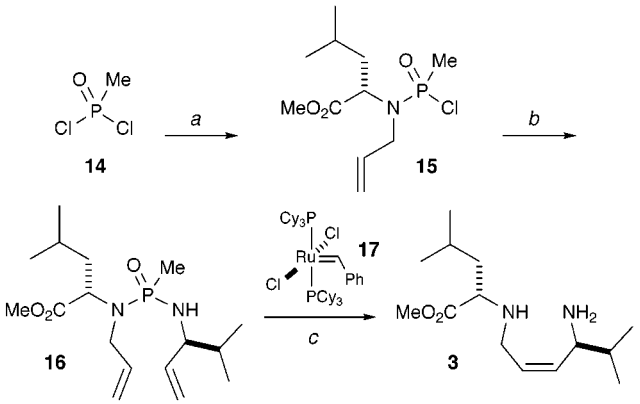


[a] Reagents and conditions: (a) $RP(O)Cl_2$ (**12a**,R = OPh; **12b**, R = Ph), Et_3N, DMAP, CH_2Cl_2, reflux, R = OPh, >95%, R = Ph, 84%; (b) i. **9**, benzene, reflux, ii. HCl/H_2O/THF, 50 °C, R = OPh, 91%, R = Ph, 70%.

was crucial in the synthesis of diamine **2** to use $RP(O)Cl_2$ (R ≠ Cl), where R serves as an ancillary blocking group to prevent the formation of the triply coupled product. Subsequent RCM using catalyst **9**, followed by in situ hydrolysis of the P(V)-tether under slightly more forcing conditions (50 °C), generates 1,4-diamine **2**.

To extend the scope of utilizing temporary *P*-tethers, we directed our efforts toward the synthesis of unsymmetric, differentially substituted 1,4-diamines such as **3** (Scheme 4).

Scheme 4[a]



[a] Reagents and conditions: (a) **7a**, Et_3N, DMAP, CH_2Cl_2, reflux, >95%, ds = 1.1:1.0;[24] (b) **11**, Et_3N, DMAP, CH_2Cl_2, 0 °C, 88%, ds = 6.6−13.2:1.0; (c) i. **17**, CH_2Cl_2, reflux, ii. methanolic HCl, 50 °C, 97%.

Prior work in our laboratory revealed that only 1 equiv of an *N*-allylated, α-branched amino ester, such as **7a**, couples with P(V)-dichlorides, such as methylphosphonic dichloride (**14**), to give an ∼1.1:1.0 diastereomeric mixture of phosphonamidic monochloridates **15**.[24] We reasoned that this monochloridate, **15**, would serve as an ideal intermediate in the production of the differentially substituted 1,4-diamine **3**. Therefore, addition of primary amine **11** to the diastere-

(15) For the first generation Grubbs catalyst, see: (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. For the second generation Grubbs catalyst, see: (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(16) 1,3,2-Diazaphosphepine 2-oxide **10** hydrolyzed after prolonged storage at 0 °C (2−3 weeks).

(17) RCM with the traditional Grubbs benzylidene catalyst[15a,b] occurs in excellent yields with most substrates if the reaction was performed on small scale (<500 mg). Reaction times varied from 1 to 24 h.

(18) No transesterification was observed during the tether cleavage procedure when benzyl esters were employed, as in **1c** and **1d**.

(19) Details of the unsuccessful attempts with other tethers are provided in the Supporting Information.

(20) Dougherty, J. M.; Probst, D. A.; Robinson, R. E.; Moore, J. D.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron* **2000**, *56*, 9781−9790 and references therein.

(21) (a) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676−678. (b) Saari, W. S.; Fisher, T. E. *Synthesis* **1990**, 453−454.

(22) (a) Unpublished results from our laboratory. Our findings are in agreement with Wills and co-workers who have reported that 3 equiv of (*R*)-α-methyl benzylamine couple readily with $POCl_3$ to provide the corresponding phosphoramide, see: (b) Burns, B.; Studley, J. R.; Wills, M. *Tetrahedron Lett.* **1993**, *34*, 7105−7106.

(23) This is in sharp contrast with our report that the addition of α-branched secondary amines such as **7** to $POCl_3$ occurs only once to give the phosphonamidic dichloridate, see ref 6b.

(24) Sprott, K. T.; Hanson, P. R. *J. Org. Chem* **2000**, *65*, 4721−4728.

omeric mixture of **15** produces the unsymmetric metathesis precursor **16** in high yield and with good to high diastereoselectivity (ds 6.6−13.2:1.0).[25] Metathesis utilizing the first generation Grubbs catalyst[15a,b] **17**, followed by in situ acid-mediated methanolic cleavage of the P(V)-tether, affords unsymmetric 1,4-diamine **3** in near quantitative yield.

The strengths of this new *P*-tether strategy are reflected in the ease in which the chiral, nonracemic 1,4-diamines can be synthesized. Not only is the RCM/hydrolysis sequence a single-pot event but chromatography is required only after the initial phosphorus/amine coupling. Moreover, the 1,4-diamines **1**−**3** can be obtained in high purity by simple acid/base extraction following the cleavage of the temporary *P*-tether (>99% purity as determined by GC and >95% purity as determined by ^{1}H, ^{13}C, and ^{31}P NMR analysis). We have demonstrated the efficacy of this sequence by generating as much as 10 g of 1,4-diamines **1b** in a single afternoon starting from *N*-allylated amino esters **7b**.

In summary, we have developed an efficient method to synthesize C_2-symmetric and unsymmetric, nonracemic 1,4-diamines **1**−**3** via a *P*-tethered RCM/hydrolysis sequence, of which the P(III)-tether represents the first of its kind.[10] To our knowledge, this approach represents the first synthetic pathway that allows for the expedient coupling of two amines via a facile temporary tether approach. Furthermore, we have demonstrated the *P*-tether strategy to be an effective route to the synthesis of unsymmetric, differentially substituted 1,4-diamines. The synthetic and biological potential of the 1,4-diamines and analogues thereof is currently being investigated and will be reported in due course.

(25) The unambiguous assignment of the major diastereomer, as well as mechanistic rationale for the observed selectivity, is currently being investigated.

Acknowledgment. This investigation was generously supported by funds provided by the National Institutes of Health (National Institute of General Medical Sciences, RO1-GM58103). The authors also thank Dr. Martha Morton and Dr. David Vander Velde for their assistance with NMR measurements and Dr. Todd Williams for HRMS analysis.

Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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