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

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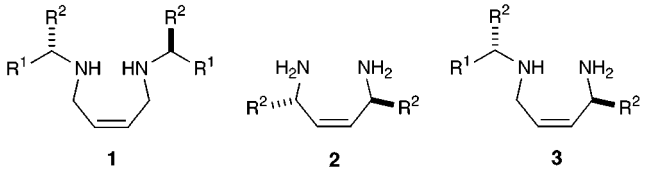
ABSTRACT



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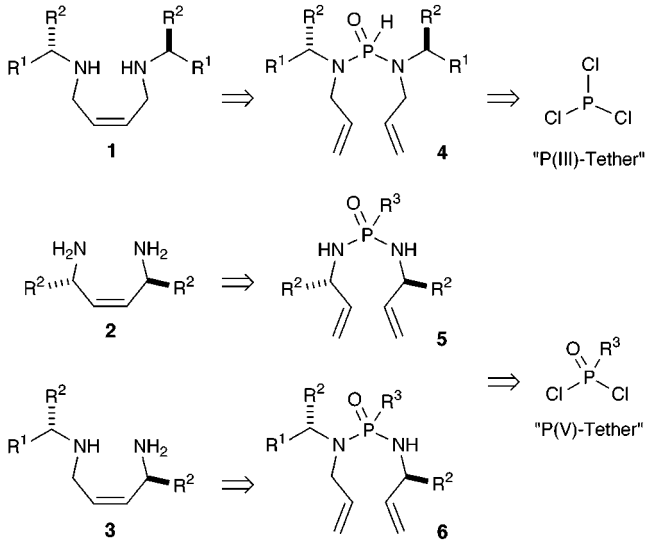
limited.[10] We now report a new strategy that allows for the rapid coupling of nonracemic allylic amines via a *P*-tether/RCM sequence[11,12] to derive *Z*-olefinic, C_2-symmetric 1,4-diamines **1** and **2** and unsymmetric, differentially substituted 1,4-diamines **3** (Scheme 1).[13]

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]

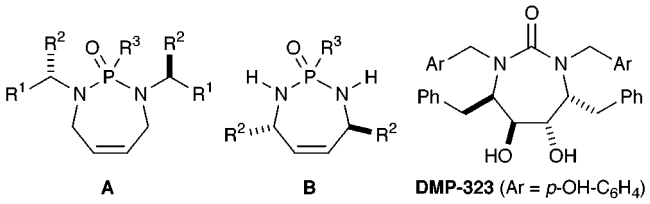
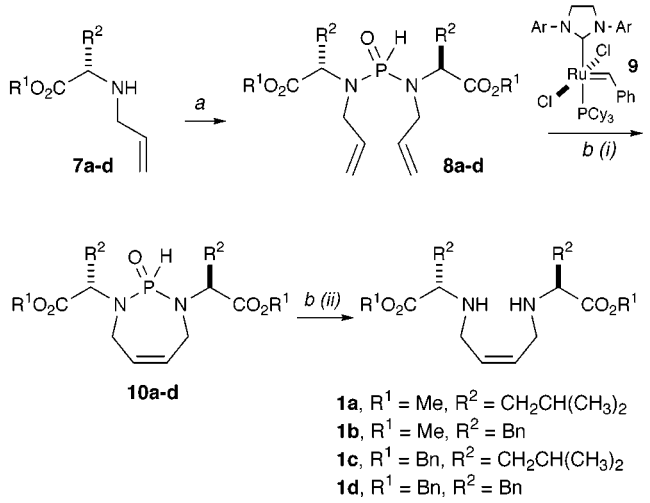


Figure 1.

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.

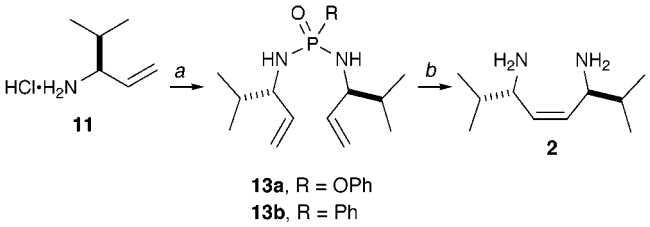
Due to the lability of the *P*−*N* bond to hydrolysis in cyclic species **10**,[16] we reasoned that we could employ the phosphorous acid diamide moiety as a P(III)-temporary tether in a one-pot RCM/hydrolysis procedure (Scheme 2). Optimization of the previously reported conditions[6b] provides acyclic 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]

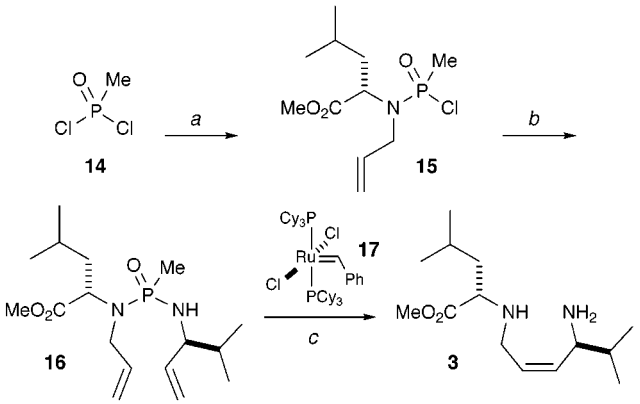


[a] Reagents and conditions: (a) $RP(O)Cl_2$ (**12a**,R = OPh; **12b**, R = Ph), Et_3N, DMAP, CH_2Cl_2, reflux, R = OPh, >95%, R = Ph, 84%; (b) i. **9**, benzene, reflux, ii. HCl/H_2O/THF, 50 °C, R = OPh, 91%, R = Ph, 70%.

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.

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

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