Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4825–4829

Comparative approaches toward diamines containing spatially separated homobenzylic and benzylic nitrogen stereocenters

Michal Achmatowicz,* Johann Chan, Philip Wheeler, Longbin Liu and Margaret M. Faul

Chemistry Process Research and Development, Amgen Inc., One Amgen Center Dr., Thousand Oaks, CA 91320, USA

Received 29 March 2007; accepted 11 May 2007
Available online 18 May 2007

Abstract—Several synthetic strategies to diamines **1**–**3** are described. The optimum approach via opening of aziridine afforded **1**–**3** in 29–60% yield over 3–5 steps. A study on formation of the benzylic stereocenter using Toste's rhenium-catalyzed asymmetric reduction of phosphinyl ketimines was also evaluated and afforded **15** in 92% de.

Inhibition of the MAP kinase p38 has been implicated in the treatment of arthritis and other inflammatory diseases.[1] Our medicinal chemistry team identified the homobenzylic–benzylic diamine motifs **1**–**3** (Fig. 1) as a key structural feature of several potent p38 inhibitors.[2] While benzylic and homobenzylic amines are common pharmacophores found among active pharmaceutical ingredients,[3] their syntheses remain a challenge. Herein we disclose our investigations toward an optimal synthesis of chiral diamines **1**–**3** containing two spatially separated nitrogen stereocenters.[4]

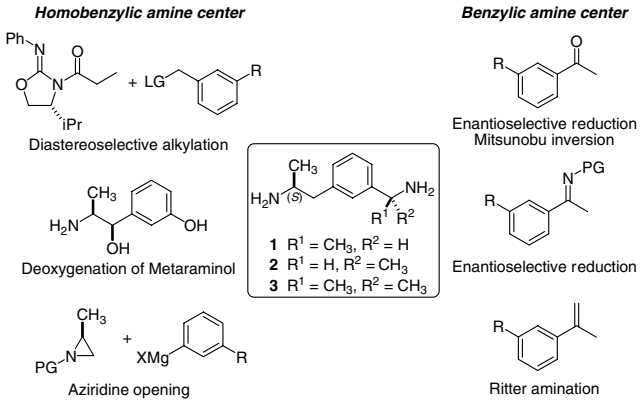
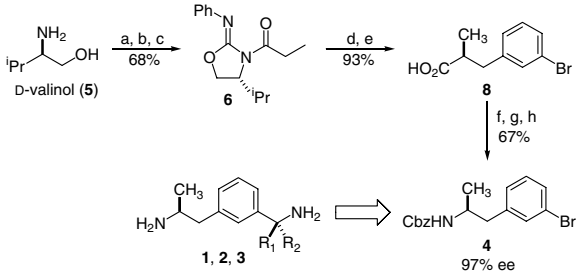


Figure 1. Different approaches to setting the homobenzylic and the benzylic stereochemistry.

The common feature of diamines **1**–**3** is the (*S*)-configured homobenzylic stereogenic center, which we initially envisaged to arise via diastereoselective alkylation of an appropriate propionate followed by a Curtius rearrangement. We proposed that the secondary benzylic center would be introduced by enantioselective reduction of the corresponding ketone or imine. In the case of **3**, a benzylic Ritter-type reaction would afford the corresponding *gem*-dimethyl product.

Our original route to diamines **1**–**3** took advantage of the readily available amine **4** (Scheme 1) that was suitable for SAR studies. The chiral N-protected



Scheme 1. Diastereoselective alkylation approach to setting the homobenzylic stereocenter. Reagents and conditions: (a) PhNCS, THF, rt; (b) TsCl, aq NaOH, THF, rt, 91% (2-step yield); (c) KO^{t}Bu, EtCOCl, THF, rt, 75%; (d) LiHMDS, *m*-bromobenzyl bromide (**7**), THF, −78 °C, >99% de, 99%; (e) NaOH, dioxane, 100 °C, 93%; (f) EtOCOCl, TEA, THF, 0 °C to rt; (g) aq NaN_3, 0 °C to rt; (h) BnOH, dioxane, toluene, 110 °C, 96.7% ee, 67% (3-step yield).

* Corresponding author. E-mail: michala@amgen.com

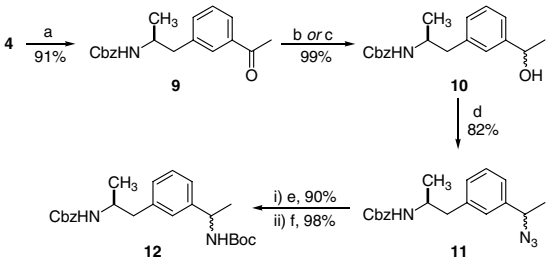
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.073

homobenzylic amine **4** was synthesized via an 8-step sequence starting from D-valinol (**5**). Thus enantiomerically pure **5** was converted, using literature methods,[5] into an Evans-type chiral auxilliary[6] followed by acylation with propionyl chloride to afford **6** in 68% yield. A chelation-controlled diastereoselective alkylation of the lithium (*Z*)-enolate of **6**, using *meta*-bromobenzyl bromide (**7**) followed by hydrolytic removal and recycling of the chiral auxilliary (98% recovery), produced enantiomerically pure acid **8**.[7] Curtius rearrangement followed by trapping of the intermediary isocyanate with benzyl alcohol provided enantiomerically enriched **4** (97% ee). This synthetic sequence provided sufficient quantities of **4** in 42% overall yield (Scheme 1).[8]

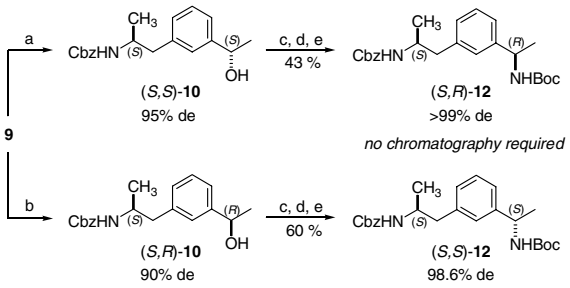
Our initial attempts to set the benzylic amine center in compounds **1**–**3** focused on accessing acetophenone **9** (Scheme 2). The treatment of **4** with 1 mol % $Pd(OAc)_2$, 2.2 mol % dppp, 1.2 equiv K_2CO_3, and 2.5 equiv *n*-butyl vinyl ether in 8.5 vol. DMF/water (5:1)[9] at 80 °C afforded ketone **9** in 91% yield after aqueous workup and recrystallization (0.1 kg scale).[10]

To set the benzylic stereogenic center present in **1** or **2**, ketone **9** was diastereoselectively reduced using either (*S*)-CBS or (*R*)-CBS reagents to afford *N*-Cbz-protected aminoalcohols (*S*,*S*)-**10** (95% de) and (*S*,*R*)-**10** (90% de), respectively (Scheme 2). Alcohols **10** were separately carried through the sequence starting with a Mitsunobu inversion using hydrazoic acid,[11] zinc reduction of the resulting azide **11**, followed by protection of the resulting amine as the *N*-Boc derivative **12**. Each of the above sequences from ketone **9** to the orthogonally protected diastereomeric diamines **12** was optimized, allowing the 4-steps to be performed with a single isolation (Scheme 3). Final purification by recrystallization afforded both (*S*,*R*)-**12** (43% yield,[12] >99% de) and (*S*,*S*)-**12** (60% yield,[12] >98.5% de) in excellent yield over 4-steps on a multigram scale.

An alternative approach to introduction of the chiral phenethylamine moiety utilized the method of diastereoselective imine reduction, recently published by Toste and co-workers.[13] The required diphenylphosphinyl ketimine was prepared according to literature procedures.[14] Quantitative formation of the oxime from



Scheme 2. Conversion of aryl bromide **4** to orthogonally protected diamine **12**. Reagents and conditions: (a) 1 mol % $Pd(OAc)_2$, 2.2 mol % dppp, K_2CO_3, *n*-butyl vinyl ether, DMF/water 5:1, 80 °C, 91%; (b) 5 mol % (*S*)-CBS, THF, −14 °C, 99% (*S*,*S*)-**10** (95% de); (c) 5 mol % (*R*)-CBS, THF, −14 °C, 99% (*S*,*R*)-**10** (90% de); (d) DIAD, TPP, HN_3, CH_2Cl_2, −20 °C to rt, 82%; (e) Zn, NH_4Cl, EtOH, 60 °C, 90%; (f) Boc_2O, CH_2Cl_2, rt, 98%.

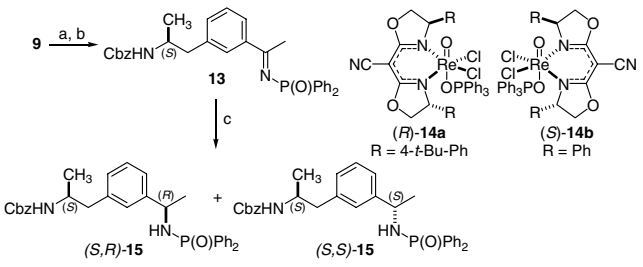


Scheme 3. Telescoped sequence from **9** to (*S*,*R*)-**12** and (*S*,*S*)-**12**. Reagents and conditions: (a) 5 mol % (*S*)-CBS, THF, −14 °C, 95% de; (b) 5 mol % (*R*)-CBS, THF, −14 °C, 90% de; (c) DIAD, TPP, HN_3, CH_2Cl_2, −20 °C to rt; (d) Zn, NH_4Cl, EtOH, 80 °C; (e) Boc_2O, CH_2Cl_2, rt, 43–60% 4-step yield.

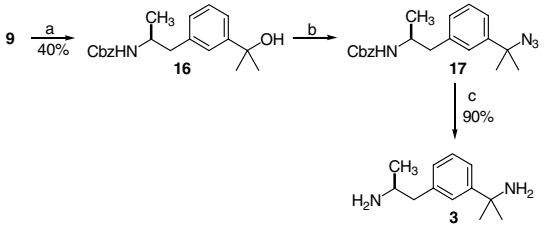
ketone **9** followed by reaction with chlorodiphenylphosphine at low temperature (−40 °C) afforded a reactive intermediate[15] that was subsequently rearranged to required diphenylphosphinyl ketimine **13** (64% yield) (Scheme 4). Reduction of **13** was attempted in the presence of 3 mol % rhenium catalysts (*R*)-**14a** or (*S*)-**14b** with phenyldimethylsilane (DPMS-H) as the stoichiometric reductant (Scheme 4).

In contrast to several similar ketimines studied by Toste and co-workers,[13,16] reduction of **13** with catalyst (*R*)-**14a** suffered poor reactivity (77%, 88% de) leading to a mixture of *N*-Dpp-amines **15** after 5 days at room temperature. Interestingly replacing dichloromethane with 1,2-dichloroethane did not improve the reactivity; however, it resulted in a markedly increased diastereoselectivity (95% de). A similar trend was observed with a less elaborated but more readily available catalyst (*S*)-**14b**. However, the diastereoselectivities were not synthetically useful (50% de). Ultimately, we found that increasing the reaction temperature in 1,2-dichloroethane had little effect on diastereoselectivity. Thus using (*R*)-**14a** as catalyst reaction at 70 °C for 3 days gave 86% conversion to (*S*,*R*)-**15**[17] with 92% de.

Initial attempts at formation of the *gem*-dimethyl diamine **3** began with the addition of a methyl anion equivalent to ketone **9** to afford tertiary alcohol **16** followed by a Ritter-type reaction with hydrazoic acid.[11,18] However, a low yield was observed upon addition of



Scheme 4. Catalytic diastereoselective reduction of *N*-diphenylphosphinyl ketimine using chiral rhenium complexes. Reagents and conditions: (a) NH_2OH, MeOH, rt, 99%; (b) Ph_2PCl, TEA, −40 °C to rt, 64%; (c) 3 mol % (*R*)-**14a** or (*S*)-**14b**, 2 equiv $PhMe_2SiH$, chlorinated solvent, rt or 70 °C.



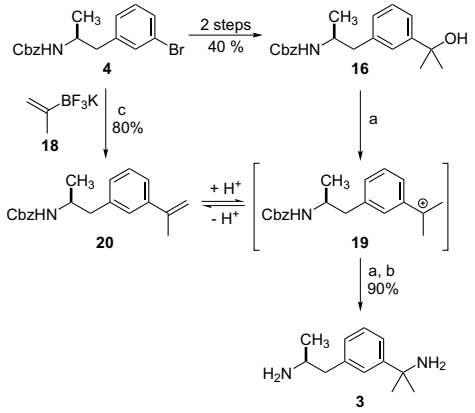
Scheme 5. Initial approach to **3**. Reagents and conditions: (a) MeMgBr, THF, −20 °C, 40%; (b) HN_3, TFA, toluene, rt; (c) H_2, Pd–C, rt, 90% 2-step yield.

MeMgBr presumably due to enolization of ketone **9** (Scheme 5).[19]

Therefore, an alternative approach to **3** targeted 1,1-disubstituted olefin **20**. Coupling of aryl bromide **9** with potassium *iso*-propenyltrifluoroborate (**18**)[20] afforded Ritter reaction substrate **20** in 80–84% yield (Scheme 6).

Hydrazoic acid addition to **20**, followed directly by hydrogenation, afforded **3** in 90% overall yield. Having established several viable routes to the benzylic amine we focused our attention back to obtain a more concise synthesis toward the homobenzylic amine.

Beginning with commercially available metaraminol (**21**),[3] elaboration to diamine **3** was accomplished via a

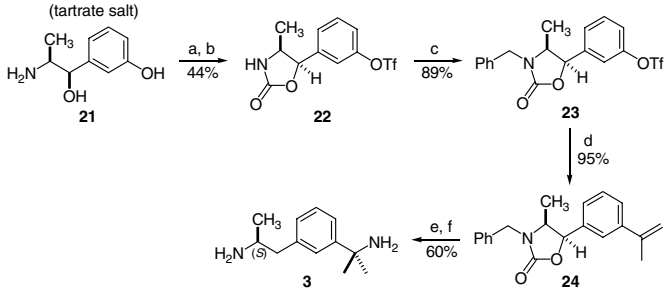


Scheme 6. Alternative approach to **3** via olefination strategy. Reagents and conditions: (a) HN_3, TFA, toluene, rt; (b) H_2, Pd–C, rt; (c) 1 mol % $Pd(dppf)Cl_2$, 2 mol % diisopropylamine, K_2CO_3, *n*-PrOH, 90 °C.

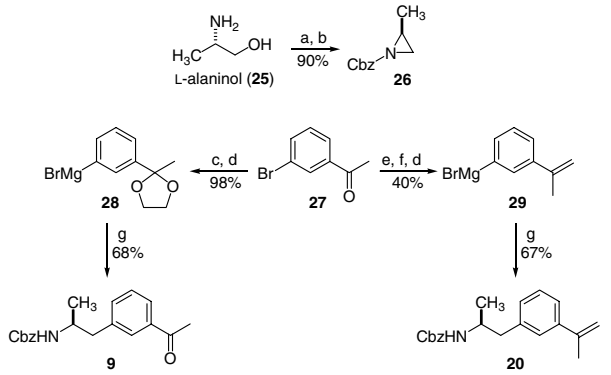
6-step sequence (Scheme 7). Carbonylation of metaraminol using phosgene followed by treatment with triflic anhydride afforded **22** in 44% yield over 2 steps. Protection of the cyclic carbamate (as the *N*-Bn derivative **23**, 89% yield) allowed a clean cross coupling with potassium *iso*-propenyltrifluoroborate (**18**) to afford 1,1-disubstituted olefin **24** in 95% yield. Finally, treatment of **24** with hydrazoic acid gave the azide that upon hydrogenation in the presence of Pearlmann's catalyst afforded diamine **3** in 60% yield over 2 steps.

Readily available enantiopure aziridines[21,22] in principle offer a convergent way to construct the homobenzylic amine portion of **1**–**3** by a ring opening with appropriate aryl carbanions. However, carbanions generally exhibit poor reactivities toward ring opening reactions unless an activating, electron-withdrawing group is present on the aziridine nitrogen atom.[23] The most prevalent activating group employed has been the *N*-tosyl,[21,24] but this can be difficult to remove. Aziridines with more easily removable groups, such as *N*-Boc,[21] have seldom been used due to poor reactivity[25] and side-reactions,[26] with the notable exception of *N*-Dpp-aziridines introduced by Sweeney and co-workers.[27] In our search for a convergent route toward **1**–**3**, we decided to investigate conditions that favor aziridine ring opening over side-reactions within the *N*-substituent. Our first choice was *N*-Cbz-protected aziridine (**26**) derived from L-alaninol (**25**). The advantages of the Cbz group over other viable *N*-substituents such as Dpp were twofold: (i) the reaction would afford the same *N*-Cbz-protected intermediates (**9** or **20**) for which further chemistry had already been developed (vide infra); (ii) orthogonal protection would be retained, as compared with *N*-Dpp-aziridines which would likely need a re-protection (cf. imine reduction approach, Scheme 4).

The *N*-Cbz-protected aziridine **26** was prepared using analogous one-pot procedure developed for *N*-Boc-aziridines[22c] in 90% yield. The carbon nucleophiles, in this case functionalized aryl Grignard reagents **28** or **29**, were prepared from commercially available 3-bromoacetophenone (**27**) (Scheme 8). Reaction of aziridine **26** with aryl cuprates, generated in situ from a copper salt (0.05–1.0 equiv) and arylmagnesium bromides (1.1–2.0 equiv) at −20 °C, led predominantly to ring opening with complete regioselectivity toward the less substituted carbon. All identified side-products were



Scheme 7. Metaraminol deoxygenation-Ritter strategy toward diamine **3**. Reagents and conditions: (a) phosgene, aq KOH, toluene; (b) Tf_2O, pyridine, 44% 2-step yield; (c) NaH, BnBr, THF, rt, 89%; (d) **18**, 1 mol % $Pd(dppf)Cl_2$, 2 mol % diisopropylamine, K_2CO_3, *n*-PrOH, 90 °C, 95%; (e) HN_3, TFA, toluene, rt; (f) 14 bar H_2, 5% $Pd(OH)_2$, EtOAc, rt, 60% 2-step yield.



Scheme 8. Homobenzylic amines via copper(I) catalyzed aziridine opening strategy. Reagents and conditions: (a) CbzCl, CH_2Cl_2, aq $NaHCO_3$, rt; (b) TsCl, KOH, Et_2O, reflux, 90% (2-step yield); (c) ethylene glycol, cat. PTSA, toluene, reflux, 98%; (d) Mg, cat. 1,2-dibromoethane, THF, 35–40 °C to rt; (e) MeMgBr, Et_2O, THF, −5 °C; (f) 10 mol % MsOH, neat, 85 °C, 40% (2-step yield); (g) 0.9 equiv **26** (limiting reagent), 10 mol % CuI, 10 mol % P(*n*-Bu)$_3$, −20 °C, then aq NH_4Cl, 62–68%.

derived from the attack of the arylmagnesium (**28** or **29**) on the carbonyl of the Cbz-group. Surprisingly, cuprates generated from the respective organolithiums were not competent in the ring opening reaction. These results suggest that lithium cations[28] are the cause of this dramatic change in the reactivity of aziridines. By using Grignard reagents as cuprate precursors, homobenzylic amines **9** and **20** were isolated in good yields (68% and 67%, respectively). Homobenzylic amine **9** was elaborated to the desired **1** or **2** using the CBS reduction/azide displacement/reduction protocol (cf. Scheme 3). Overall, diamines **12**[29] were prepared in a respectable 29–41% yield over 5-steps from readily available aziridine **26**. *gem*-Dimethyl amine **3** was prepared in 60% yield over 3-steps from **26**.

In summary, several approaches to diamines **1**–**3** containing spatially separated stereocenters have been demonstrated. An approach utilizing an aziridine ring opening with aryl cuprates afforded the desired amines **1**–**3** in high overall yield. Key to the ring opening of aziridines was the exclusion of lithium cations. Further studies are currently ongoing.

Acknowledgments

We are indebted to Professor Dean Toste for providing samples of the rhenium complexes (*R*)-**14a** and (*S*)-**14b**. We would like to thank Aaron Siegmund, Patricia Lopez, Mike Frohn, and Gilbert Rishton for their early-stage contributions to this work.

References and notes

1. For a review, see: Schieven, G. L. *Curr. Top. Med. Chem.* **2005**, *5*, 921.
2. (a) Lopez, P.; Siegmund, A.; Frohn, M.; Liu, L. Rishton, G. unpublished results; (b) Frohn, M. J.; Hong, F.-T.; Liu, L.; Lopez, P.; Siegmund, A. C.; Tadesse, S.; Tamayo, N. WO 070932A2, 2005, Amgen Inc.
3. Homobenzylic amines are present in Aramine® (metaraminol, **21**) (antihypotensive), Cetapril® (antihypertensive), Dofetilide® (antiarrythmic), Edepryl® (antiparkinsonia), Foradil® (bronchpdilator), OxyContin® (analgesic); Benzylamines are found in Taxotere® (anticancer), Zoloft® (anxiolytic), Lamisil® (antibiotic), Sensipar® (renal failure).
4. Compounds **1** and **2** contain two stereogenic centers, whereas **3** contains one homobenzylic amine stereocenter and a benzylic quaternary center.
5. Kim, T. H.; Lee, N.; Lee, G.-J.; Kim, J. N. *Tetrahedron* **2001**, *57*, 7137–7141.
6. Facile cleavage and recycling are the main advantages of this chiral auxiliary over the standard Evans' oxazolidinone system.
7. Lee, G.-J.; Kim, T. H.; Kim, J. N.; Lee, U. *Tetrahedron: Asymmetry* **2002**, *13*, 9–12.
8. Average of multiple runs.
9. Vallin, K. S. A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 4340–4343.
10. 80% of **9** isolated by crystallization. Additional 11% of **9** could be recovered from the mother liquors by column chromatography (91% yield total).
11. Caution: Hydrazoic acid is a volatile and potentially explosive compound in a gaseous state. Handle with care. Avoid contact with heavy metal salts and alloys.
12. First crop. Additional material could be recovered by chromatography of the mother liquors.
13. Nolin, K. A.; Ahn, R. W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 12462–12463.
14. Krzyzanowska, B.; Stec, W. J. *Synthesis* **1982**, 270–273; Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634–5635.
15. *O*-Diphenylphosphinyl oxime. Unstable *O*-phosphinyl oximes (cf. Lopez, L.; Barrans, J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1806–1811) rearrange thermally to *N*-phosphinyl imines via the radical mechanism (cf. Brown, C.; Hudson, R. F.; Maron, A.; Record, K. A. F. *J. Chem. Soc., Chem. Commun.* **1976**, 663–664).
16. Typical reaction time reported in Ref. 13 was 72 h at room temperature.
17. The stereochemistry of the major product was not assigned. However, the stereochemistry shown in Scheme 4 follows the direction of the induction from Ref. 13.
18. (a) Balderman, D.; Kalir, A. *Synthesis* **1978**, 24–26; (b) Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, *49*, 4237–4244.
19. Addition of Cu^I salts or anhydrous $CeCl_3$ to mitigate these issues was not investigated.
20. (a) Molander, G. A.; Rivera, M. R. *Org. Lett.* **2002**, *4*, 107–109; (b) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424–8429.
21. For recent reviews on aziridine chemistry, see: (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743; (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347–1365.
22. (a) Giles, P. R.; Roger-Evans, M.; Soukup, M.; Knight, J. *Org. Process Res. Dev.* **2003**, *7*, 22–24; (b) Travins, J. M.; Etzkorn, F. A. *Tetrahedron Lett.* **1998**, *39*, 9389–9392; (c) Wessig, P.; Schwarz, J. *Synlett* **1997**, 893–894; (d) Baldwin, J. E.; Farthing, C. N.; Rusell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett.* **1996**, *37*, 3761–3764.
23. Aziridines are preferentially ring-opened by soft, heteroatom-based nucleophiles (Ref. 21). For the most recent examples, see: (a) Wu, J.; Sun, X.; Sun, W. *Org. Biomol. Chem.* **2006**, *4*, 4231–4235; (b) Wu, J.; Sun, X.; Sun, W.; Ye, S. *Synlett* **2006**, 2489–2491; (c) Liu, P.; Forbeck, E.

M.; Evans, C. D.; Joullié, M. M. *Org. Lett.* **2006**, *8*, 5105–5107; (d) Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2005**, *7*, 3509–3512; (e) Reddy, M. S.; Rao, K. R. *Synlett* **2005**, 489–490.

24. (a) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Tetrahedron* **2005**, *61*, 9586–9593; (b) Cox, P.; Craig, D.; Ioannidis, S.; Rahn, V. S. *Tetrahedron Lett.* **2005**, *46*, 4687–4690; (c) Cunha, R. L. O. R.; Diego, D. G.; Simonelli, F.; Comasseto, J. V. *Tetrahedron Lett.* **2005**, *46*, 2539–2542; (d) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Synlett* **2004**, 1691–1694, For the earlier examples, see: Ref. 21.
25. Large excess of Grignard reagents were required: Ref. 22b (2.5–5.0 equiv), Ref. 22d (3.5–10.1 equiv), Osowska-Pacewicka, K.; Zwierzak, A. *Synthesis* **1996**, 333–335 (2–3 equiv). These methods are economically viable only if a carbon nucleophile is inexpensive and readily available.
26. Attack of the nucleophile on the carbamate carbonyl (*N*-Boc or *N*-Cbz) or phosphorus atom in the *N*-diphenylphosphinyl group (*N*-Dpp) (Ref. 27a).
27. (a) Cantril, A. A.; Osborn, H. M. I.; Sweeney, J. *Tetrahedron* **1998**, *54*, 2181–2208; (b) Osborn, H. M. I.; Sweeney, J. B. *Tetrahedron Lett.* **1994**, *35*, 2739–2742; (c) Osborn, H. M. I.; Sweeney, J. B. *Synlett* **1994**, 145–147.
28. Solubilization of copper salts effected by anhydrous lithium salts (LiCl or LiBr) also led to inactive copper species.
29. Compounds (*S*,*S*)-**12** and (*S*,*R*)-**12** are orthogonally protected diamines **1** and **2**, respectively.