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Diversity-Oriented Synthesis of Azaspirocycles

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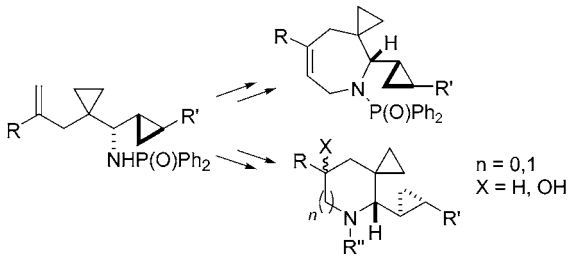
ABSTRACT



Multicomponent condensation of *N*-diphenylphosphinoylimines, alkynes, zirconocene hydrochloride, and diiodomethane provides a rapid access to ω-unsaturated dicyclopropylmethylamines. These novel building blocks are converted into heterocyclic 5-azaspiro[2.4]heptanes, 5-azaspiro-[2.5]octanes, and 5-azaspiro[2.6]nonanes by means of selective ring-closing metathesis, epoxide opening, or reductive amination. The resulting functionalized pyrrolidines, piperidines, and azepines are scaffolds of considerable relevance for chemistry-driven drug discovery.

Multicomponent reactions allow rapid access to structurally varied and increasingly complex intermediates or scaffolds. These reactions present an opportunity to explore combinatorial chemistry approaches for the synthesis of a diverse set of target molecules from simple, readily available building blocks.[1]

We have reported a number of new multicomponent condensations and cascade reactions involving vinyl zirconocenes,[2] dihaloalkanes, and *N*-diphenylphosphinoyl imines leading to allylic,[3] homoallylic,[4] *C*-cyclopropyl-,[3,5] and *C*,*C*-dicyclopropylmethyl amides[6] in a highly regio- and stereoselective fashion. For example, hydrozirconation[7] of alkyne **1** initiated a sequenced reaction cascade leading to *C*,*C*-dicyclopropylmethyl amide **3** with the concomitant formation of 10 new C,C-bonds (Figure 1). The conversion

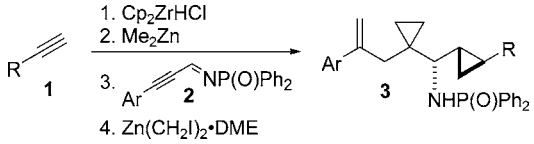


Figure 1. One-pot preparation of *C*,*C*-dicyclopropylmethylamines.

of **1** and **2** to **3** proceeds under mild conditions by repeated methylene group transfers to intermediate bicyclo[1.1.0]-butanes and 1,4-dienes.[6]

As demonstrated herein, this methodology has now been extended to include the transformation of alkynyl phosphinamides where alkenylzinc addition is no longer the initiating step in the cascade. After addition of Me_2Zn, the phosphinamides **4** and **5** are treated with $Zn(CH_2I)_2$·DME complex and afford the *C*-cyclopropylalkylamides **6** and **7** in good

(1) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471.
(2) Wipf, P.; Nunes, R. L. *Tetrahedron* **2004**, *60*, 1269.
(3) (a) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761. (b) Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449. (c) Wipf, P.; Kendall, C. *Chem. Eur. J.* **2002**, *8*, 1778.
(4) Wipf, P.; Kendall, C. *Org. Lett.* **2001**, *3*, 2773.
(5) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122.
(6) Wipf, P.; Stephenson, C. R. J.; Okumura, K. *J. Am. Chem. Soc.* **2003**, *125*, 14694
(7) (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (b) Lipshutz, B. H.; Pfeiffer, S. S.; Tomioka, T.; Noson, K. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; p 110.

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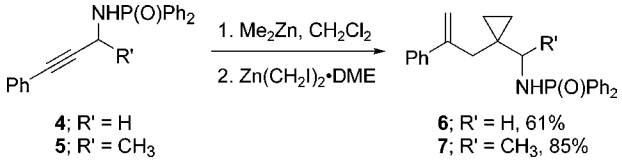
yield (Scheme 1).[8] This extension further generalizes our strategy for the preparation of *C*-cyclopropylalkylamides and allows direct access to these interesting functional groups independent of the availability of imines **2** or alkynes **1**.

Scheme 1. Preparation of *C*-Cyclopropylalkylamides from Propargyl Phosphinamides



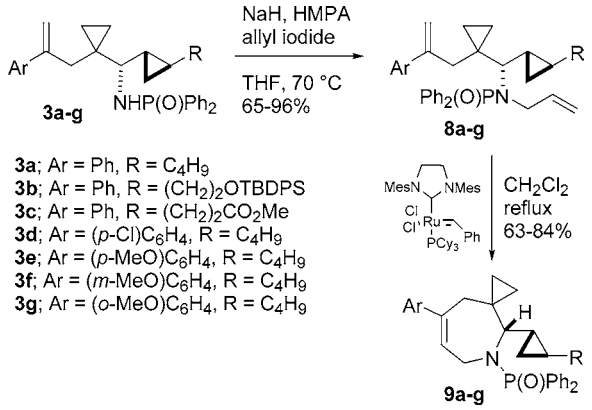
4; R' = H
5; R' = CH_3

6; R' = H, 61%
7; R' = CH_3, 85%

Recently, it has been demonstrated that molecular flexibility in biological screening samples is often associated with increased metabolism and decreased bioavailability.[9] In addition to minimizing this risk by cyclizing cyclopropylalkylamides **3**, **6**, and **7**, we were interested in expanding the structural diversity of these novel building blocks by selectively converting them into common 5-, 6-, and 7-membered heterocyclic scaffolds used for biological screens.[10]

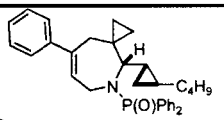
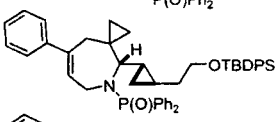
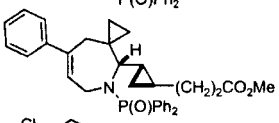
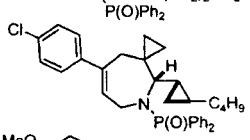
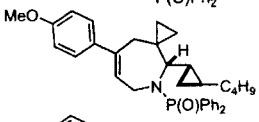
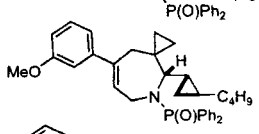
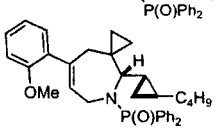
Indeed, we were able to take advantage of the functional groups in **3**, **6**, and **7** for the straightforward preparation of spirocyclic azepines, piperidines, and pyrrolidines. Although *N*-heterocycles are often present in natural products and pharmaceutically useful compounds, these azaspirocyclic scaffolds represent novel structures for biological evaluation. Ring-closing metathesis precursors **8a**−**g**[11,12] were readily available in 65 to 96% yield via *N*-alkylation (NaH, HMPA, allyl iodide) of phosphinamides **3a**−**g**. While the ring-closing event using 10 mol % of Grubbs' second generation catalyst[13] was rapid in dichloroethane,[12a] alkene isomerization to the enamide was competitive (azepine/enamide ~1:1).[12b,14] However, this undesired isomerization pathway could be minimized by lowering the reaction temperature (CH_2Cl_2, reflux) leading to the desired 1*H*-azepines **9a**−**g** in 63−84% yield (Scheme 2). Functionalization was tolerated on both the arene segment as well as the alkyne side chain, and no ring opening of cyclopropanes was observed (Table 1).[15]

Scheme 2. Azepine Formation by Sequential *N*-Allylation/Ring-Closing Metathesis



3a; Ar = Ph, R = C_4H_9
3b; Ar = Ph, R = $(CH_2)_2$OTBDPS
3c; Ar = Ph, R = $(CH_2)_2CO_2Me$
3d; Ar = (*p*-Cl)C_6H_4, R = C_4H_9
3e; Ar = (*p*-MeO)C_6H_4, R = C_4H_9
3f; Ar = (*m*-MeO)C_6H_4, R = C_4H_9
3g; Ar = (*o*-MeO)C_6H_4, R = C_4H_9

Table 1. Conversions of *C*,*C*-dicyclopropylmethylamines **3** into Azepines **9** According to Scheme 2

entry	yield of **8** [%][a]	azepine **9**	yield of **9** [%][a]
1	95		75
2	88		71
3	65		63
4	75		72
5	69		80
6	96		75
7	89		84

[a] Yield of isolated products.

We also envisioned the preparation of smaller nitrogen-containing heterocycles using a reductive amination strategy. The ω-disubstituted alkene moiety in **3** and **6** was easily converted to an aryl ketone under Johnson−Lemieux[16] conditions (Scheme 3). We were unable to affect reductive amination under Lewis acidic conditions (BF_3•OEt_2/Ph_3SiH[17] or $TiCl_4$/Et_3SiH), but a simple three-step, one-pot protocol involving *N*-deprotection (HCl/MeOH) followed by reductive amination ($NaBH_3CN$, MeOH) and acylation (AcCl, DIPEA)

(8) $Zn(CH_2I)_2$•DME was used for mmole-scale preparations of *C*,*C*-dicyclopropylmethylamides **3**, **6**, and **7** as a safer alternative to $Zn(CH_2I)_2$ without noticeable attenuation of reactivity. Cf. Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081.

(9) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45*, 2615.

(10) Lee, M.-L.; Schneider, G. *J. Comb. Chem.* **2001**, *3*, 284.

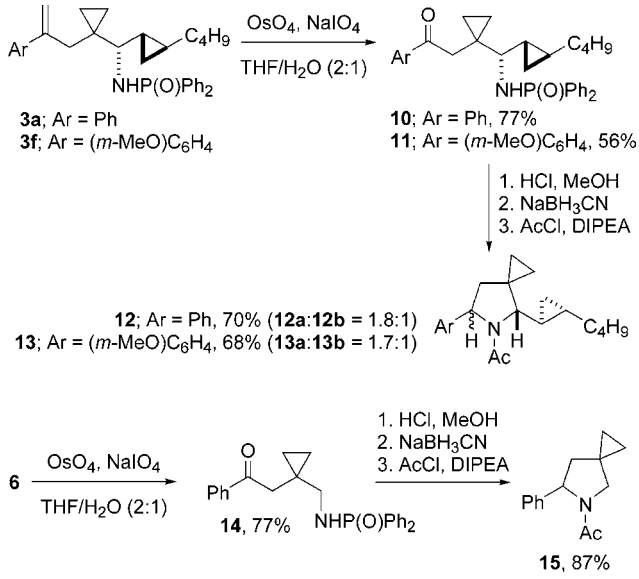
(11) (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(12) For the preparation of azepines by ring-closing metathesis, cf. (a) Hoffmann, T.; Waibel, R.; Gmeiner, P. *J. Org. Chem.* **2003**, *68*, 62. (b) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848. (c) Furstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811. (d) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324.

(13) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(14) (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390. (b) Lehman, S. E., Jr.; Schwendeman, J. E.; O'Donnell, P. M.; Wagener, K. B. *Inorg. Chim. Acta* **2003**, *345*, 190. (c) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414.

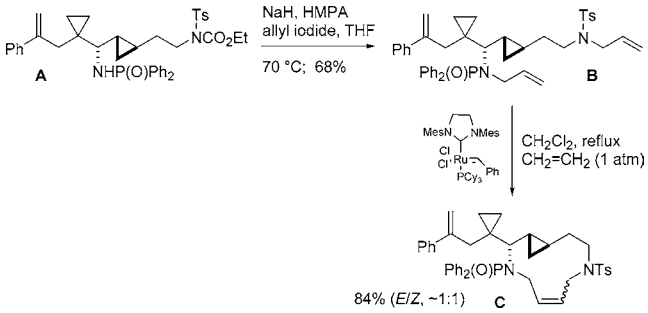
Scheme 3. Reductive Amination Approach to Pyrrolidines



afforded the desired pyrrolidines in good yield. While the diastereoselectivity of the reductive amination step was poor,[18] the diastereomers were readily separated by column chromatography.

In addition to the formation of 5- and 7-membered azaspirocycles, piperidines could be obtained via the 6-*endo* opening of epoxides **16** and **17** (Scheme 4).[19] After epoxidation of **6** and **7**, cyclization under basic conditions afforded the desired piperidines **18** and **19**, respectively. The latter compound was formed as a mixture of diastereomers originating from a lack of selectivity in the epoxidation step. Interestingly, the more highly substituted epoxides **20** and

(15) Exposure of **A** to the allylation conditions led to carbamate cleavage product **B**, which upon ring-closing metathesis provided the 11-membered **C** rather than the azepine product. Interestingly, this reaction was much faster (<1 h) than the formation of azepines **9**.



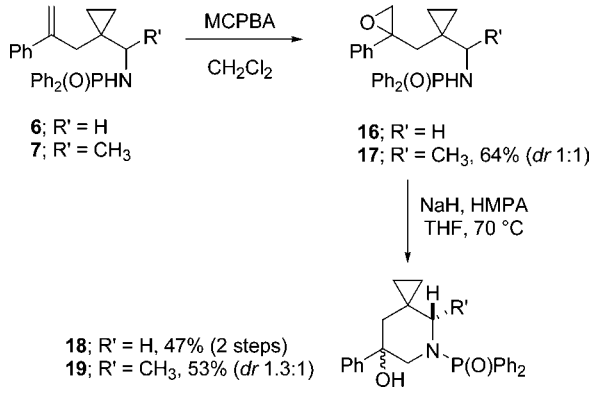
(16) (a) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478. (b) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.

(17) Rudolph, A. C.; Machauer, R.; Martin, S. F. *Tetrahedron Lett.* **2004**, *45*, 4895.

(18) These observations are in agreement with the results of Rudolph et al. (ref 17); however, Lewis acidic conditions appear to promote *N*-dephosphinoylation and do not furnish the desired pyrrolidines in acceptable yields.

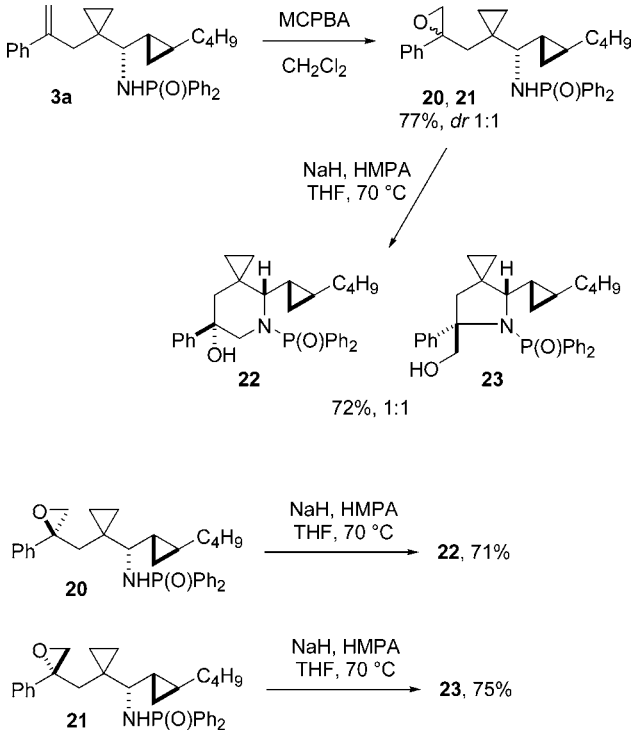
(19) (a) LaLonde, R. T.; Muhammad, N.; Wong, C. F.; Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664. (b) Nuhrich, A.; Moulines, J. *Tetrahedron* **1991**, *47*, 3075. (c) Breternitz, H.-J.; Schaumann, E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1927. (d) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583.

Scheme 4. Piperidine Synthesis via 6-*Endo* Epoxide Opening



21 derived from *C*,*C*-dicyclopropylmethylamine **3a** cyclized stereospecifically to yield piperidine **22** and pyrrolidine **23**, respectively (Scheme 5). Individual reactions of the chro-

Scheme 5. Stereospecific Formation of Pyrrolidines and Piperidines by Intramolecular Epoxide Aminolysis



matographically separated, pure epoxides confirmed that 6-*endo* cyclization of **20** led to **22** as a single reaction product, as expected based on steric hindrance and the precedence of **16** and **17**, while diastereomer **21** afforded exclusively the 5-*exo* cyclization product pyrrolidine **23**.

At this time, we can only speculate about the origin of the stereospecificity of the intramolecular aminolysis of **20** and **21**, but the steric influence of the substituent α to the nitrogen atom clearly plays a role since it reverses the inherent 6-*endo* selectivity in the case of the 1,4-*syn* diastereomer **21**.[20]

In summary, we have extended the multicomponent condensation of alkenylzirconocenes with *N*-diphenylphosphinoyl imines and diiodomethane to the direct cyclopropanation−rearrangement of readily available alkynyl phosphinamides. The resulting *C*-[1-(2-arylallyl)cyclopropyl]-alkylamines **3**, **6**, and **7** provide valuable starting points for the diversity-oriented synthesis of heterocycles. Functionalized pyrrolidines, piperidines, and azepines are easily accessible in 2−3 steps in good overall yields. Further applications of the Zr → Zn transmetalation/multicomponent condensation methodology as well as the biological evaluation[21] of new azaspirocycles will be reported in due course.

Acknowledgment. This work has been supported by NIH P50-GM067082.

Supporting Information Available: Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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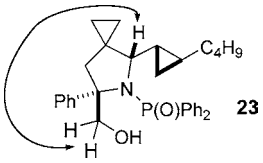
(20) The relative stereochemistry of **23** was assigned by NOESY and the product was assumed to arise from an inversion of configuration at the quaternary carbon atom.



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(21) Preliminary screening of compounds **3** revealed interesting nuclear receptor binding and antiproliferative effects.