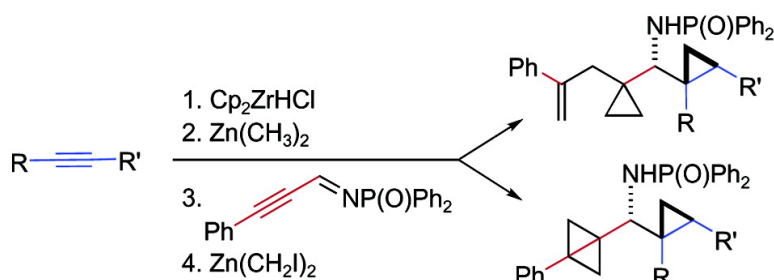


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*J. Am. Chem. Soc.*, **2003**, 125 (48), 14694-14695 • DOI: 10.1021/ja038623a • Publication Date (Web): 06 November 2003

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## Transition-Metal-Mediated Cascade Reactions: C,C-Dicyclopropylmethylamines by Way of Double C,C- $\sigma$ -Bond Insertion into Bicyclobutanes

Peter Wipf,\* Corey R. J. Stephenson, and Kazuo Okumura

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received September 19, 2003; E-mail: pwipf@pitt.edu

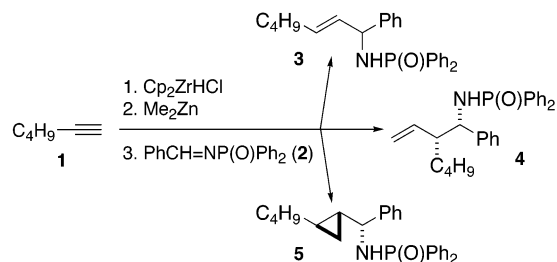
The multicomponent cascade reactions of organozirconocenes reveal novel reaction manifolds that culminate in the stereoselective formation of multiple C,C-bonds and allow the rapid assembly of complex and diverse products from simple building blocks.<sup>1</sup> In toluene, the dimethylzinc-mediated addition of alkenylzirconocenes to diphenylphosphinoyl imines leads to allylic amine **3**; in contrast, in the presence of  $\text{CH}_2\text{I}_2$  or when  $\text{CH}_2\text{Cl}_2$  is used as the solvent, the reaction provides homoallylic amine **4** or *C*-cyclopropylalkylamine **5** (Scheme 1).<sup>2</sup> While organolithium and Grignard reagents suffer from poor functional group tolerance, the hydrozirconation<sup>3</sup> of alkynes is selective in the presence of many electrophilic groups, and the intermediate alkenylzirconocenes can be added to aldehydes,<sup>4</sup> ketones,<sup>5</sup> enones,<sup>6</sup> epoxides,<sup>7</sup> esters,<sup>8</sup> isocyanates,<sup>9</sup> and nitrones.<sup>10</sup>

Recently, we discovered that the addition of hexenylzirconocene to alkynyl imine **6** in the presence of dimethylzinc and the zinc carbenoid  $\text{Zn}(\text{CH}_2\text{I})_2$ <sup>11</sup> leads to *C,C*-dicyclopropylmethylamines **7** as single diastereomers in 60% yield (Scheme 2). During the course of this unprecedented cascade process, 10 C,C-bonds are formed (nine remain in the product), while two C,C-bonds are broken, including the alkyne triple bond in imine **6**! Upon reaction optimization, we were able to decrease the amount of  $\text{Cp}_2\text{ZrHCl}$ ,  $\text{Me}_2\text{Zn}$ , and alkyne significantly and increase the yield to 68% when dichloroethane was used as the solvent (Table 1, entry 4).<sup>12</sup>

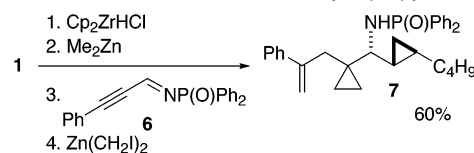
For a further investigation of the scope of this new reaction, a series of alkynes and alkynylamines<sup>13</sup> were subjected to the optimized reaction conditions (Table 2). The methodology tolerates a number of the common protecting groups used in synthesis such as silyl ethers, carbamates and sulfonamides, as well as silyl and ortho esters.<sup>14</sup> Interestingly, when internal alkynes are used, the rare bicyclobutane scaffold is obtained upon quenching at 0 °C (entries 9–11).

Reexposure of allylic amine and bicyclobutane to the reaction conditions led to the formation of the corresponding *C,C*-dicyclopropylmethylamines. Accordingly, the formation of the bicyclobutane intermediate provides valuable evidence for the mechanistic pathway of this cascade process (Figure 1). Upon transmetalation of the alkenylzirconocene to dimethylzinc, addition to the imine proceeds to give **30**. Alkyl group exchange generates the zinc carbenoid **31** which undergoes triple cyclopropanation at the allylic alkene as well as the alkyne moiety to give the bicyclo[1.1.0]butane **32**. These reactive intermediates are known to undergo a double  $\sigma$ -bond insertion with carbenes, thus producing the skipped diene **33**; however, prior work<sup>15</sup> has been limited to unfunctionalized model systems, and no synthetically useful application of the double  $\sigma$ -bond insertion process has been reported. A final cyclopropanation of the allylic amine, undoubtedly assisted by the metalated proximal amide, affords **34**.<sup>16</sup> The relative configuration of all alkynyl imine adducts was assigned on the basis of ref 2a.

**Scheme 1.** Reaction Manifolds in Zirconocene Additions to Imines

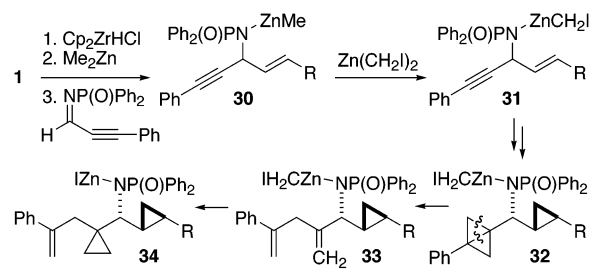


**Scheme 2.** One-Pot Formation of *C,C*-Dicyclopropylmethylamine



**Table 1.** Optimization of the Formation of **7** from Alkyne **1** and Imine **6**

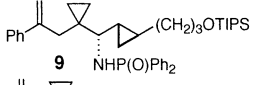
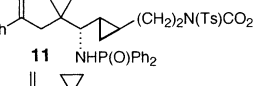
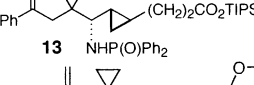
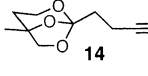
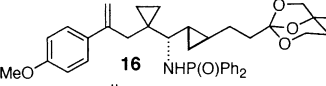
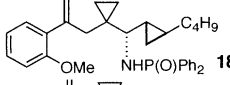
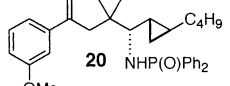
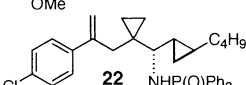
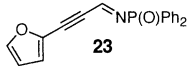
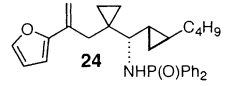
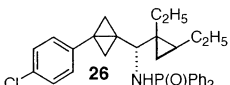
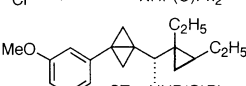
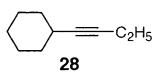
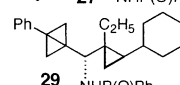
entry	equiv of $\text{Cp}_2\text{ZrHCl}$	equiv of <b>1</b>	equiv of $\text{Me}_2\text{Zn}$	equiv of $\text{Zn}(\text{CH}_2\text{I})_2$	solvent	temp [°C]	yield [%]
1	3	3	3	3	$\text{CH}_2\text{Cl}_2$	rt	60
2	1.5	1.5	1.5	4	toluene	rt	<50
3	1.5	1.5	1.5	4	$(\text{CH}_2\text{Cl})_2$	rt	60
4	1.5	1.5	1.5	4	$(\text{CH}_2\text{Cl})_2$	0	68



**Figure 1.** Proposed mechanism.

In summary, we have been able to demonstrate a novel organometallic multicomponent reaction that represents the first synthetically useful example of a double C,C- $\sigma$ -bond insertion.<sup>17</sup> This reaction proceeds under mild conditions via the rare bicyclo[1.1.0]butanes, and the increase in structural complexity from starting materials is highlighted by the formation of nine new C,C-bonds in the final product. The unprecedented *C,C*-dicyclopropylmethylamine scaffold can now be prepared diastereoselectively in a single step, allowing for the preparation of structurally diverse compounds from readily available starting materials. Studies of the biological profile of *C,C*-dicyclopropylmethylamines and further

**Table 2.** Multicomponent Condensation of Alkynes, Imines, and Zinc Carbenoids to Give *C,C*-Dicyclopropylmethylamines

Entry	Alkyne	Imine	Product	Yield [%] <sup>a</sup>
1	TIPSO(CH <sub>2</sub> ) <sub>3</sub> -≡ <b>8</b>	<b>6</b>		66
2	EtO <sub>2</sub> C(Ts)N(CH <sub>2</sub> ) <sub>2</sub> -≡ <b>10</b>	<b>6</b>		43
3	TIPSO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> -≡ <b>12</b>	<b>6</b>		55
4		<i>(p</i> -MeO)Ph-≡-NP(O)Ph <sub>2</sub> <b>15</b>		44
5	<b>1</b>	<i>(o</i> -MeO)Ph-≡-NP(O)Ph <sub>2</sub> <b>17</b>		52
6	<b>1</b>	<i>(m</i> -MeO)Ph-≡-NP(O)Ph <sub>2</sub> <b>19</b>		50
7	<b>1</b>	<i>(p</i> -Cl)Ph-≡-NP(O)Ph <sub>2</sub> <b>21</b>		58
8	<b>1</b>			47
9	C <sub>2</sub> H <sub>5</sub> -≡-C <sub>2</sub> H <sub>5</sub> <b>25</b>	<b>2 1</b>		51
10	<b>2 5</b>	<b>1 9</b>		53
11		<b>6</b>		55 <sup>b</sup>

<sup>a</sup> Yields of isolated products are based upon imines. <sup>b</sup> Microwave conditions.

investigations of unique reactivity patterns in the combination of Zr and Zn chemistry will be reported in due course.

**Acknowledgment.** This work was supported by the National Science Foundation (CHE-0078944).

**Supporting Information Available:** Experimental procedures, <sup>1</sup>H and <sup>13</sup>C spectra for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- Wipf, P.; Kendall, C. *Chem.-Eur. J.* **2002**, *8*, 1778.
- (a) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761. (b) Wipf, P.; Kendall, C. *Org. Lett.* **2001**, *3*, 2773.
- (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.
- (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454. (c) Wipf, P.; Jayasuriya, N.; Ribe, S. *Chirality* **2003**, *15*, 208. (d) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965.
- (a) Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449. (b) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667.
- (a) Loots, M. J.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045. (b) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440. (c) Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, *56*, 6494.
- Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 825.
- Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 5880.
- Negishi, E.; Swanson, D. R.; Miller, S. R. *Tetrahedron Lett.* **1988**, *29*, 1631.
- Pandya, S. U.; Garcon, C.; Chavant, P. Y.; Py, S.; Vallée, Y. *Chem. Commun.* **2001**, 1806.
- (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. (b) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1. (c) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.
- The lifetime of the alkenylzinc reagent generated under these conditions is significantly shorter in CH<sub>2</sub>Cl<sub>2</sub>, and excess reagent is required: Wipf, P.; Kendall, C., unpublished results.
- Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561.
- Wipf, P.; Xu, W.; Kim, H.; Takahashi, H. *Tetrahedron* **1997**, *53*, 16575.
- (a) Jackson, J. E.; Mock, G. B.; Tetef, M. L.; Zheng, G.-X.; Jones, M., Jr. *Tetrahedron* **1985**, *41*, 1453. (b) Wiberg, K. B.; Lampman, G. M.; Ciula, R. P.; Connor, D. S.; Schertler, P.; Lavanish, J. *Tetrahedron* **1965**, *21*, 2749. (c) Applequist, D. E.; Wheeler, J. W. *Tetrahedron Lett.* **1977**, *18*, 3411. (d) Doering, W. von E.; Coburn, J. F., Jr. *Tetrahedron Lett.* **1965**, *6*, 991. (e) Turner, R. B.; Goebel, P.; Doering, W. von E.; Coburn, J. F., Jr. *Tetrahedron Lett.* **1965**, *6*, 997.
- Deuterium-labeling experiments with Zn(CD<sub>2</sub>)<sub>2</sub> led to incorporation of five CD<sub>2</sub> groups into **7**, thus supporting the mechanism shown in Figure 1.
- For examples of single C,C-bond insertions, see: (a) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 871. (b) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976.

JA038623A