5122 *J. Am. Chem. Soc.* **2001,** *123,* 5122−5123

Three-Component Aldimine Addition−Cyclopropanation. An Efficient New Methodology for Amino Cyclopropane Synthesis

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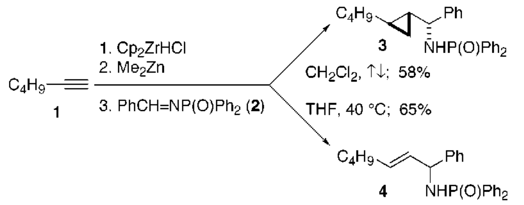
Received March 2, 2001
Revised Manuscript Received April 12, 2001

The hydrozirconation of alkenes and alkynes is one of the most versatile and direct pathways for the formation of organometallic intermediates for organic synthesis.[1] Due to the steric shielding of the C−Zr bond by the cyclopentadienyl ligands, however, many applications of organozirconocenes have been limited to oxidative cleavage with halogens. In addition to chloride abstractions with silver(I) salts and subsequent cascade processes initiated by formally cationic zirconocenes,[2] transmetalation of the C−Zr bond to other metal salts is an effective way to utilize the potential of the organozirconocene intermediate for carbon−carbon bond formation.[1] We have previously developed a protocol for Zr → Zn transmetalation that allows in situ addition to aldehydes and, in the presence of a chiral ligand, the enantioselective preparation of allylic alcohols.[3] We now report an extension of this transmetalation strategy toward the three-component condensation of organozirconocenes, aldimines, and dihalomethanes and the stereoselective formation of amino cyclopropanes.

Hydrozirconation of 1-hexyne (**1**) in CH_2Cl_2 with Schwartz reagent followed by in situ transmetalation to Me_2Zn and addition of *N*-diphenylphosphinoylimine **2**[4] provided the *trans*-amino cyclopropane **3** in 58% yield and the allylic amide **4** in 11% yield after heating the reaction mixture at reflux for 16 h (Scheme 1).[5] In contrast, when the reaction was performed in THF, a 65% yield of **4** was obtained as the sole product.[6] We rationalized this novel solvent-dependent reaction dichotomy by the formation of a transient zinc-carbenoid species from CH_2Cl_2, which subjected the intermediate allylic amine derivative to an efficient Simmons−Smith type[7] cyclopropanation. *N*-Metalation of the phosphinoylamine moiety from the 1,2-addition step was clearly crucial for the ensuing Simmons−Smith process, since control experiments showed that only a protocol involving deprotonation of **4** with BuLi followed by treatment with Me_2Zn and addition to vinylzirconocene in CH_2Cl_2 led to further conversion to **3**. In the absence of BuLi, neutral **4** remained unchanged.

Scheme 1



Interestingly, the presence of dimethyl zinc alone in the absence of zirconocene is also not sufficient for effecting cyclopropanation, since the hexenyl zinc derivative obtained from **1** via hydroboration−transmetalation[8] in CH_2Cl_2 did not convert **2** to **3**.[9] Control experiments in different solvents, at lower temperatures, and at shorter reaction times confirmed that 1,2-addition preceded the cyclopropanation and that no cyclopropyl zinc species[10] were formed prior to imine addition.[11] In analogy to recent results by Charette and co-workers,[12] we therefore propose the mechanism shown in Figure 1. Hydrozirconation of the alkyne followed by transmetalation to dimethyl zinc leads to an alkenyl zinc species that readily adds to the phosphinoylimine to give allylic amide **5**. While the facile formation of the zinc carbenoid species **6** from **5** and dichloromethane is unprecedented,[13] the intrinsically high reactivity of (chloromethyl)zinc derivatives is well-known,[14] and an amide nitrogen has been shown to be a powerful directing group[15] for Wittig−Furukawa reagents.[16]

To improve on the yield and the rate of the transformation of **1** to **3**, we added 5 equiv of CH_2I_2 to the reaction mixture and were able to obtain the desired amino cyclopropane in 74% yield after 2 h in refluxing CH_2Cl_2. Under these optimized conditions, functionalized terminal and internal alkynes were converted to amino cyclopropanes in moderate to high yields and with excellent diastereoselectivity (Table 1).

Traces of unreacted allylic amine intermediates were the only identifiable side products, but no stereoisomeric cyclopropanes could be identified in ^{1}H NMR analyses of crude reaction mixtures. The transformation enjoys a significant functional group tolerance, since silyl ethers (entries 3 and 7), silyl esters (entry 4), and carbamate or sulfonamide functions (entry 5) in the alkyne segment do not interfere. Significantly, internal alkyne **8** provided trisubstituted cyclopropane **9** (entry 2). Both electron-donating (entry 9) and electron-withdrawing substitutents (entries 6, 7, and 8) in the benzaldimine portion are tolerated. The yields based on imine range from 45% for the highly functionalized alkyne **14** to 84% in the addition to ester-substituted **16**, which is remarkable considering that three C,C-bonds and one C,H-bond are formed stereoselectively during the three-component condensation process. The alkynyl imine **23** led to cyclopropane adduct **24** in 44% yield, thus illustrating that the presence of an aromatic substituent at the imine carbon is not essential for the process. *N*-Phosphi-

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[1] Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853.

[2] (a) Wipf, P.; Aslan, D. C. *J. Org. Chem.* **2001**, *66*, 337. (b) Wipf, P.; Tsuchimoto, T.; Takahashi, H. *Pure Appl. Chem.* **1999**, *71*, 415. (c) Suzuki, K. *Pure Appl. Chem.* **1994**, *66*, 1557.

[3] (a) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454. (b) Wipf, P.; Xu, W.; Takahashi, H.; Jahn, H.; Coish, P. D. G. *Pure Appl. Chem.* **1997**, *69*, 639. (c) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197.

[4] For precedence for the addition of organozinc species to *N*-diphenylphosphinoylimines, see: (a) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097. (b) Suzuki, T.; Shibata, T.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2757. (c) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530. (d) Jimeno, C.; Reddy, K. S.; Sola, L.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 3157. For relevant imine reviews, see: (e) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (f) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (g) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.

[5] The relative stereochemistry of **3** was determined by X-ray analysis of a *p*-nitrobenzoyl derivative of **25**.

[6] In the absence of Me_2Zn, no reaction took place in either solvent.

[7] (a) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1.

[8] Srebnik, M. *Tetrahedron Lett.* **1991**, *32*, 2449.

[9] Instead, allylic amide **4** was isolated in 49% yield.

[10] Yachi, K.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2515.

[11] Use of CD_2Cl_2 as a solvent led to geminal bisdeuterated cyclopropane, thus confirming that the solvent served as carbene precursor.

[12] Charette, A. B.; Francoeur, S.; Martel, J.; Wilb, N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4539.

[13] Both CH_2I_2 and CH_2Br_2 have been utilized in the Simmons−Smith reaction, but CH_2Cl_2 is generally considered unreactive in a wide range of modifications of this method: Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. (b) LeGoff, E. *J. Org. Chem.* **1964**, *29*, 2048. (c) Maeda, T.; Tada, H.; Yasuda, K.; Okawara, R. *J. Organomet. Chem.* **1971**, *27*, 13. (d) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 892. It has, however, been reported that a mixture of alkene and methylene chloride reacts with heated zinc film at low pressure to give traces of cyclopropane products: Faveau, C.; Gault, Y.; Gault, F. G. *Tetrahedron Lett.* **1967**, 3149.

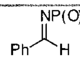
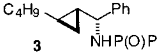
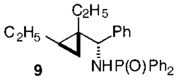
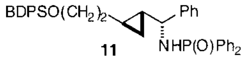
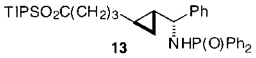
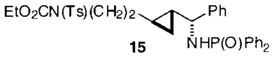
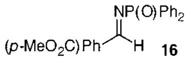
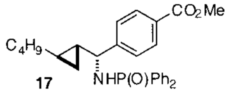
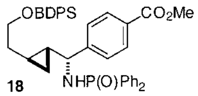
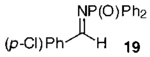
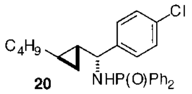
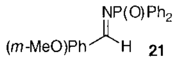
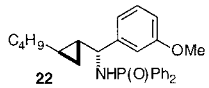
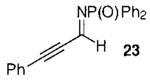
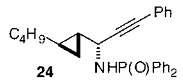
[14] Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974. It is possible that the zirconocene derivative obtained from transmetalation to Me_2Zn facilitates carbenoid formation from CH_2Cl_2.

[15] Russ, P.; Ezzitouni, A.; Marquez, V. E. *Tetrahedron Lett.* **1997**, *38*, 723.

[16] The observed *anti*-selectivity of cyclopropane formation is surprising, given the generally strong preference for *syn*-selective cyclopropanation of allylic alcohols: Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3944.

10.1021/ja0157494 CCC: $20.00

Table 1. Three-Component Condensation of Alkynes, Benzaldimines, and CH_2I_2

entry	alkyne	imine	amino cyclopropane	yield[a]
1	$C_4H_9{-}{\equiv}$ **1**	 **2**		74%
2	$C_2H_5{-}{\equiv}{-}C_2H_5$ **8**	**2**		46%
3	$BDPSO(CH_2)_2{-}{\equiv}$ **10**	**2**		68%
4	$TIPSO_2C(CH_2)_3{-}{\equiv}$ **12**	**2**		73%
5	$EtO_2CN(Ts)(CH_2)_2{-}{\equiv}$ **14**	**2**		45%
6	**1**	 **16**		69%
7	**10**	**16**		84%
8	**1**	 **19**		65%
9	**1**	 **21**		51%
10	**1**	 **23**		44%

[a] Yields of isolated products are based on imines.

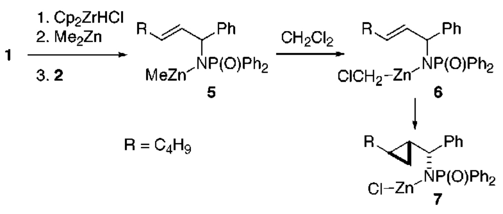
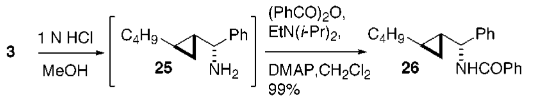


Figure 1. Proposed mechanism.

Scheme 2



noylimines derived from α,*β*-unsaturated aldehydes such as cinnamaldehyde and α-methylcinnamaldehyde, however, provided complex mixtures of mono- and biscyclopropanated products. Attempts to prepare *N*-phosphinoylimines derived from enolizable aldehydes, such as hydrocinnamaldehyde, failed.[17]

The *N*-phosphinoylamino cyclopropane products are readily deprotected to give free amino cyclopropanes by acid hydrolysis (Scheme 2).[18] Prior alternative protocols for the preparation of these versatile building blocks for organic synthesis have been quite limited in scope.[19]

In conclusion, the three-component condensation of in situ prepared alkenyl zirconocenes, aldimines, and CH_2X_2 highlights many fundamentally new aspects of organo-zirconocene and zinc chemistry. For the first time, CH_2Cl_2 has been proven to be an effective agent for cyclopropanation in the Simmons−Smith reaction. While CH_2Cl_2 currently needs to be used as a solvent and does not quite match the reactivity of CH_2I_2, it is nonetheless intriguing that in a reaction medium containing Me_2Zn, a metalated allyl phosphinoylamine, and zirconocene complex, a reactive zinc carbenoid species is readily obtained by zinc insertion into the C,Cl-bond of CH_2Cl_2. The present work also reveals the strong directing and possibly activating effects of *N*-diphenylphosphinoylamines in the cyclopropanation reaction.[20] Finally, a novel application of in situ prepared alkenyl zirconocenes was demonstrated that provides new methodology and significant functional group tolerance for the synthesis of amino cyclopropanes. A simple switch in reaction solvents from CH_2Cl_2 to THF allows the isolation of intermediate allylic amines, which are by themselves important organic building blocks.[21,22] Studies toward enantioselective variants of zirconocene-mediated allylic amine and amino cyclopropane syntheses are currently underway in our laboratories and will be reported in due course.

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

Supporting Information Available: Experimental procedures,^1H and ^{13}C NMR spectra for all new compounds, and X-ray structure of the *p*-nitrobenzoyl derivative of **25** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0157494

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[17] See also: Yamada, K.-i.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504.

[18] Ramage, R.; Hapton, D.; Parrott, M. J.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1357.

[19] (a) Tomilov, Y. V.; Kostitsyn, A. B.; Shulishov, E. V.; Nefedov, O. M. *Synthesis* **1990**, 247. (b) Parham, W. E.; Potoski, J. R. *J. Org. Chem.* **1967**, *32*, 275.

[20] While aldehydes provide allylic alocohols under these reaction conditions,[3] no cyclopropyl alcohols are formed. However, *N*-tosyl imines undergo an analogous addition−cyclopropanation process: Kendall, C.; Wipf, P. Unpublished results.

[21] See, for example: (a) Agami, C.; Couty, F.; Evano, G. *Org. Lett.* **2000**, *2*, 2085. (b) Hollis, T. K.; Overman, L. E. *J. Organomet. Chem.* **1999**, *576*, 290. (c) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (d) Otsuka, S. *Acta Chem. Scand.* **1996**, *50*, 353.

[22] For the preparation of allylic amines from primary amines and alkynes with $Cp_2Zr(Me)Cl$, see: Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486.