Pd(0)-Catalyzed Bismetallative Cyclization of Enynes in the Presence of $Bu_3SnSiMe_3$ Using *N*-Heterocyclic Carbene as a Ligand

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Received: October 31, 2002; Accepted: December 16, 2002

Supporting information for this article is available on the WWW under http://asc-wiley-vch.de or from the author.

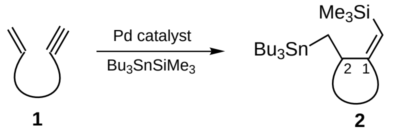
Abstract: It was found that a nucleophilic *N*-heterocyclic carbene could be utilized as a ligand for Pd(0)-catalyzed bismetallative cyclization of enynes in the presence of $Bu_3SnSiMe_3$. An imidazolium salt having a bulky alkyl group attached to both nitrogen atoms of its imidazol-2-ylidene skeleton or an imidazolinium salt is suitable as a ligand precursor. The cyclized products obtained from this cyclization have both a vinylsilane moiety and a homoallylstannane moiety, whose utility in synthetic organic chemistry has been proven by transformation into cyclopropanol derivatives.

Keywords: bismetallation; cyclization; *N*-heterocyclic carbene ligands; imidazol-2-ylidene ligands; palladium; silylstannane

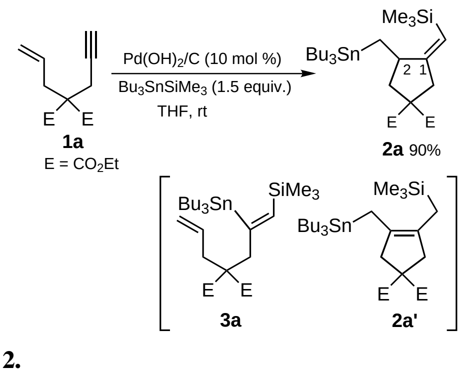
Transition metal-catalyzed addition of a bimetallic reagent to a multiple bond is of interest because new metal-carbon bonds are produced and these bonds can be utilized in further transformations as an active bimetal functional group.[1] Bismetallative cyclization between two multiple bonds might be particularly useful in synthetic organic chemistry because a cyclic compound having such an active metal-carbon bond is produced, and the cyclization of bis-dienes, diynes or enynes with a bimetallic reagent (M – M', M, M' = B, Si, Ge, Sn, etc.) has been reported.[2] We have recently reported a Pd(0)-catalyzed bismetallative cyclization of enynes in the presence of $Bu_3SnSiMe_3$, in which a cyclized product **2** having both a vinylsilane moiety and a homoallylstannane moiety was produced from enyne **1** (Scheme 1).[3]

The potential of the cyclized product as a useful synthon prompted us to try to expand this cyclization to an asymmetric synthesis by virtue of the use of a chiral ligand in the reaction. However, we encountered some difficulties. That is, a heterogeneous catalyst such as $Pd(OH)_2$ was the most efficient in this bismetallative cyclization, as we had previously reported.[3] The cyclization of **1a** with 10 mol % of $Pd(OH)_2/C$ in the presence of 1.5 equivalents of $Bu_3SnSiMe_3$ in THF at room temperature gave bismetallative cyclized product **2a** in 90% yield.

On the other hand, the use of a homogeneous catalyst or the addition of a phosphine ligand in this cyclization resulted in a decrease in the yield of the cyclized product **2a**, and the formation of a bismetallative product **3a** was increased [e.g., 3 mol % $Pd(PPh_3)_4$ in THF (at 50 °C): **2a**: 14%, **3a**: 80%; 3 mol % Pd_2dba_3/24 mol % PBu_3 in THF (at reflux): **2a**: 10%, **2a'**: 3%, **3a**: 15%; 3 mol % Pd_2dba_3/12 mol % dppp in THF (at reflux): **2a**: 15%, **2a'**: 7%, **3a**: 44%]. We therefore turned our attention to finding ligands that could be utilized in this bismetallative cyclization before the development of this reaction to an asymmetric version.

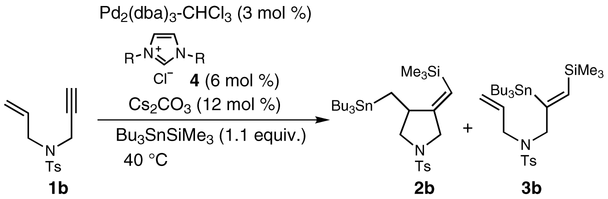


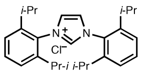
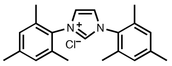
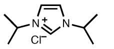
Scheme 1. Bismetallative cyclization of enyne with $Bu_3SnSiMe_3$.



Scheme 2.

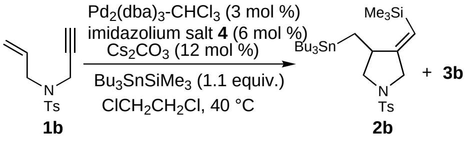
Table 1. Bismetallative cyclization of **1b** using a Pd/imidazolium salt system.

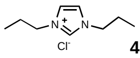
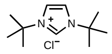
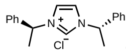


Run	Imidazolium salt **4** (R)	Solvent	Time [h]	Yield [%]		SM (**1b**) recov. [%]
				2b	3b	
1	 **4a**	THF	17	5	-	11
2	 **4b**	THF	17	5	2	19
3	 **4c**	THF	20	21	2	10
4	**4c**	DMF	24	-	2	47
5	**4c**	CH_3CN	15	-	18	47
6	**4c**	toluene	6	33	6	-
7	**4c**	toluene[a]	7.5	36	4	7
8	**4c**	$ClCH_2CH_2Cl$	10	47	5	9
9	**4c**	$ClCH_2CH_2Cl$[a]	20	41	2	35

[a] The reaction was carried out at room temperature.

Table 2. Bismetallative cyclization of **1b** using various imidazolium salts.



Run	Imidazolium salt **4**	Time [h]	Yield [%]		SM (**1b**) recov. [%]
			2b	3b	
1	 **4d**	15	43	2	17
2	 **4e**	9	55	-	-
3	 **4f**	11	60	3	-

Recently, nucleophilic *N*-heterocyclic carbenes have attracted considerable attention not only as a stable isolable carbene species[4] but also as molecules to coordinate to various transition metals.[5] These transition metal complexes coordinated by *N*-heterocyclic carbenes were expected to have different reactivities compared with those coordinated by traditional ligands such as phosphines. In recent palladium chemistry, high catalytic efficiency has been found in a variety of reactions, including Suzuki–Miyaura coupling,[6] Kumada–Tamao–Corriu-type coupling,[7] Mizoroki–Heck reaction,[8] amination of aryl halides,[9] and Sonogashira coupling,[10] by virtue of using nucleophilic carbenes as a ligand. However, there have been no reports on Pd(0)-catalyzed bismetallative cyclization using a nucleophilic carbene as a ligand.[11] Herein we report the first application of a nucleophilic carbene as a ligand to this type of reaction.

Initially, bismetallative cyclization of enyne **1b** in the presence of $Bu_3SnSiMe_3$ was investigated using a Pd-carbene catalyst formed from $Pd_2dba_3 \cdot CHCl_3$ and various imidazolium salts **4** in the presence of Cs_2CO_3 (Table 1).[6c]

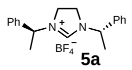
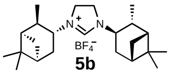
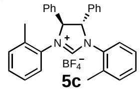
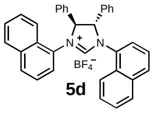
The bismetallative cyclization of **1b** in the presence of $Bu_3SnSiMe_3$ (1.1 equivalents) using a catalyst formed from $Pd_2dba_3 \cdot CHCl_3$ (3 mol %), imidazolium salt **4a** (6 mol %), and Cs_2CO_3 (12 mol %) gave the desired product **2b** in only 5% yield along with many by-products, and the starting material **1b** was recovered in 11% yield (run 1). The reaction using **4b**, which has aromatic substituents on both nitrogen atoms in its imidazole skeleton, showed a tendency similar to that using **4a**, giving **2b** in a low yield (5%) (run 2). On the other hand, the use of **4c** having alkyl groups on the nitrogen atoms improved the yield of **2b** up to 21% yield (run 3). Solvent effects were carefully examined in the bismetallative cyclization of **1b** using **4c** as an imidazolium salt. Polar solvents (DMF, CH_3CN) retarded the reaction (runs 4 and 5), and non-polar solvent (runs 6 and 7) or chlorinated solvent (runs 8 and 9) were found to be more suitable for this reaction, giving **2b** in 36% yield (toluene at room temperature, run 7) or 47% yield ($ClCH_2CH_2Cl$ at 40 °C, run 8).

Encouraged by these results, we reinvestigated the effects of substituents on the nitrogen atoms in the imidazole skeleton of imidazolium salts in the reaction of **1b** in $ClCH_2CH_2Cl$ at 40 °C (Table 2). The use of imidazolium salts **4d**–**4f** having alkyl groups on the nitrogen atoms gave good results, and the yield of **2b** reached 60% in the reaction using **4f**.[12,13]

It was found that imidazolinium salts **5**,[14] which are the saturated analogues of imidazolium salts **4**, have an equal or superior reactivity to that of **4** and that the use of **5** shortened the reaction time (Table 3). Namely, the bismetallative cyclization of **1b** using imidazolinium salt **5a** under similar conditions was completed in only 2.5 hours to give cyclized product **2b** in 50% yield (run 1). Contrary to the imidazolium salt system, it is interesting that aromatic substituents on the nitrogen atoms in the imidazoline skeleton were tolerated in this imidazolinium salt system, and the bismetallative cyclized product **2b** was obtained in 62% yield in the reaction using **5d**.[15]

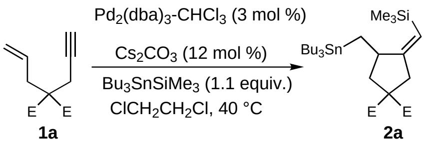
Next, the bismetallative cyclizations of **1a** were investigated under similar conditions using imidazolium salt **4f** and imidazolinium salts **5a**–**5d** (Table 4). In the case of the substrate **1a**, the use of imidazolinium salts **5** (runs 2–5) was more efficient than was the use of **4f** (run 1), and the bismetallative cyclization using **5d** under conditions similar to those described above gave

Table 3. Bismetallative cyclization of **1b** using various imidazolinium salts **5a**.[a]

Run	Imidazolinium salt **5**	Time [h]	Yield [%]	
			2b	**3b**
1	 **5a**	2.5	50	2
2	 **5b**	4.5	46	-
3	 **5c**	1.5	54	2
4	 **5d**	1.5	62	-

[a] All reactions were carried out using Pd_2dba_3-$CHCl_3$ (3 mol %), imidazoliniumu salt **5** (6 mol %), and Cs_2CO_3 (12 mol %) in the presence of $Bu_3SnSiMe_3$ (1.1 equiv.) in $ClCH_2CH_2Cl$ at 40 °C

Table 4. Bismetallative cyclization of **1a**.



Run	**4** or **5**	Time [h]	**2a** [%]
1	**4f**	36	25[a]
2	**5a**	12	58
3	**5b**	11	50
4	**5c**	16	59
5	**5d**	11	68

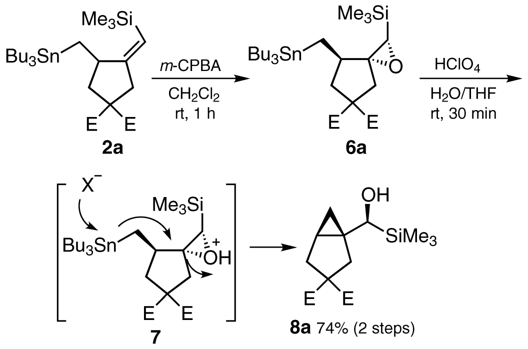
[a] **1a** was recovered in 34% yield.

bismetallative cyclized product **2a** in 68% yield (run 5).[16]

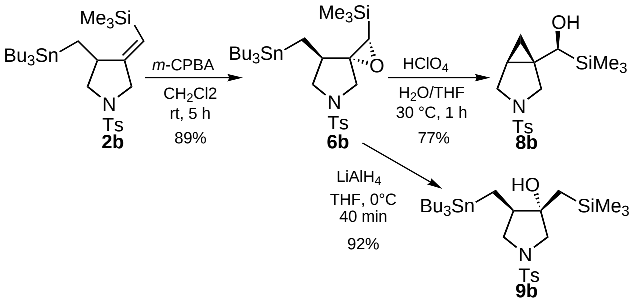
To evaluate the versatility as a synthon, transformation of the bismetallative cyclized products was investigated. Treatment of **2a** with *m*-CPBA produced epoxysilane **6a** in good yield. In this reaction, epoxidation stereoselectively occurred by attack of the reagent to the less-hindered face of vinylsilane in **2a** (Scheme 3).

When the epoxide **6a** was subjected to $HClO_4$ in H_2O-THF, a cyclopropanation reaction proceeded stereoselectively *via* intermediate **7** to give cyclopropanol derivative **8a** in 74% yield (2 steps from **2a**). Similarly, the bismetallative cyclized product **2b** could be stereoselectively converted into epoxysilane **6b**, which was also transformed into cyclopropanol **8b** (Scheme 4). On the other hand, reduction of **6b** with $LiAlH_4$ proceeded in a regio- and stereoselective manner, giving alcohol **9b** in 92% yield. These results prove the utility of the cyclized products obtained by this bismetallative cyclization.

In summary, it was found that a nucleophilic *N*-heterocyclic carbene could be utilized as a ligand for Pd(0)-catalyzed bismetallative cyclization of enynes in the presence of $Bu_3SnSiMe_3$. It has been proven that an imidazolium salt having a bulky alkyl group attached to the nitrogen atoms in its imidazol-2-ylidene skeleton or an imidazolinium salt is suitable as a ligand precursor. In addition, the cyclized products obtained from this cyclization have both a vinylsilane moiety and a homoallylstannane moiety, whose utility in synthetic organic chemistry have been proven by transformation into cyclopropanol derivatives. Although the development of this bismetallative reaction to an asymmetric version has not been achieved yet, the present study is the first in which a nucleophilic *N*-heterocyclic carbene was used as a ligand of a Pd(0) catalyst for this type of reaction. Further studies to expand the scope of this reaction and to apply this methodology to asymmetric synthesis are ongoing.



Scheme 3.



Scheme 4.

Experimental Section

Typical Procedure for Bismetallative Cyclization of 1a in the Presence of $Bu_3SnSiMe_3$ using $Pd_2(dba)_3 \cdot CHCl_3$/Imidazolinium Salt 5d/Cs_2CO_3

A solution of $Pd_2(dba)_3 \cdot CHCl_3$ (6 mg, 0.006 mmol), imidazolinium salt **5d** (7 mg, 0.012 mmol), and Cs_2CO_3 (8 mg, 0.024 mmol) in degassed $ClCH_2CH_2Cl$ (0.3 mL) was stirred at 50 °C for 10 min, and the solution was cooled to 0 °C. To the solution were added $Bu_3SnSiMe_3$ (80 μL, 0.23 mmol) and a solution of

1a (48 mg, 0.20 mmol) in $ClCH_2CH_2Cl$ (0.7 mL) at 0 °C, and the solution was stirred at 40 °C for 11 hours. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt, 100/1) to give **2a** as a colorless oil; yield: 81 mg (68%). IR (neat): $\nu = 1734, 1628, 1602, 1266, 1110$ cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 0.06$ (s, 9H), 0.78 – 0.96 (m, 6H), 0.87 (t, $J = 7.5$ Hz, 9H), 0.96 (d, $J = 12.7$ Hz, 1H), 1.06 (dd, $J = 12.7, 3.2$ Hz, 1H), 1.20 (t, $J = 6.7$ Hz, 6H), 1.17 – 1.32 (m, 6H), 1.40 - 1.52 (m, 6H), 1.69 (dd, $J = 13.3, 5.5$ Hz, 1H), 2.68 (dd, $J = 15.8, 13.3$ Hz, 1H), 2.70 (d, $J = 16.2$ Hz, 1H), 2.75 – 2.88 (m, 1H), 3.28 (dt, $J = 16.2, 2.0$ Hz, 1H), 4.16 (q, $J = 7.5$ Hz, 4H), 5.25 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$): $\delta = -0.3$, 8.8, 13.2, 13.6, 26.9, 28.8, 39.8, 42.1, 43.9, 58.0, 60.8, 60.9, 119.3, 164.9, 171.2, 171.6; EI-LRMS: $m/z = 545$ ($M^+ - t$-Bu); EI-HRMS: calcd. for $C_{24}H_{45}O_4SiSn$: 545.2109 ($M^+ - t$-Bu); found: 545.2106.

References and Notes

[1] For reviews, see: I. Beletskaya, C. Moberg, *Chem. Rev.* **1999**, *99*, 3435.

[2] For bismetallative cyclization, see: a) Y. Obora, Y. Tsuji, T. Kakehi, M. Kobayashi, Y. Shinkai, M. Ebihara, T. Kawamura, *J. Chem. Soc. Perkin Trans. 1* **1995**, 599; b) S.-y. Onozawa, Y. Hatanaka, M. Tanaka, *Chem. Commun.* **1997**, 1229; c) S.-y. Onozawa, Y. Hatanaka, N. Choi, M. Tanaka, *Organometallics* **1997**, *16*, 5389; d) M. Suginome, T. Matsuda, Y. Ito, *Organometallics* **1998**, *17*, 5233; e) M. Suginome, Y. Ito, *Chem. Rev.* **2000**, *100*, 3221; f) S. Gréau, B. Radetich, T. V. RajanBabu, *J. Am. Chem. Soc.* **2000**, *122*, 8579; g) S.-K. Kang, T.-G. Baik, A. N. Kulak, Y.-H. Ha, Y. Lim, J. Park, *J. Am. Chem. Soc.* **2000**, *122*, 11529; h) S. Shin, T. V. RajanBabu, *J. Am. Chem. Soc.* **2001**, *123*, 8416; i) M. Lautens, J. Mancuso, *Synlett* **2002**, 394.

[3] M. Mori, T. Hirose, H. Wakamatsu, N. Imakuni, Y. Sato, *Organometallics* **2001**, *20*, 1907.

[4] A. J. Arduengo, III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361.

[5] For reviews, see: a) W. A. Herrmann, *Angew. Chem. Int. Ed.* **2002**, *41*, 1290; b) W. A. Herrmann, T. Weskamp, V. P. W. Böhm, *Adv. Organomet. Chem.* **2002**, *48*, 1; c) L. Jafarpour, S. P. Nolan, *Adv. Organomet. Chem.* **2001**, *46*, 181; d) D. Bourissou, O. Guerret, F. P. Gabbaï, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39; e) W. A. Herrmann, C. Köcher, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162.

[6] a) W. A. Herrmann, C. P. Reisinger, M. Spiegler, *J. Organomet. Chem.* **1998**, *557*, 93; b) V. P. W. Böhm, C. W. K. Gstöttmayr, T. Weskamp, W. A. Herrmann, *J. Organomet. Chem.* **2000**, *595*, 186; c) C. Zhang, J. Huang, M. L. Trudell, S. P. Nolan, *J. Org. Chem.* **1999**, *64*, 3804; d) H. M. Lee, S. P. Nolan, *Org. Lett.* **2000**, *2*, 2053; e) C. Zhang, M. L. Trudell, *Tetrahedron Lett.* **2000**, *41*, 595; f) A. Fürstner, A. Leitner, *Synlett* **2001**, 290.

[7] a) J. Huang, S. P. Nolan, *J. Am. Chem. Soc.* **1999**, *121*, 9889; for Ni-catalyzed Kumada–Tamao cross-coupling reactions using nucleophilic *N*-heterocyclic carbenes, see: b) V. P. W. Böhm, T. Weskamp, C. W. K. Gstöttmayr, W. A. Herrmann, *Angew. Chem. Int. Ed.* **2000**, 39, 1602.

[8] a) W. A. Herrmann, M. Elison, J. Fischer, C. Köcher, G. R. J. Artus, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2371; b) W. A. Herrmann, J. Fischer, M. Elison, C. Köcher, G. R. J. Artus, *Chem. Eur. J.* **1996**, *2*, 772; c) D. Enders, H. Gielen, G. Raabe, J. Runsink, H. Teles, *Chem. Ber.* **1996**, *129*, 1483; d) D. S. McGuinness, M. J. Green, K. J. Cavell, B. W. Skelton, A. H. White, *J. Organomet. Chem.* **1998**, *565*, 165; e) D. S. McGuinness, K. J. Cavell, *Organometallics* **1999**, *18*, 1596; f) D. S. Clyne, J. Jin, E. Genest, J. C. Gallucci, T. V. RajanBabu, *Org. Lett.* **2000**, *2*, 1125; g) C. Yang, H. M. Lee, S. P. Nolan, *Org. Lett.* **2001**, *3*, 1511.

[9] a) J. Huang, G. Grasa, S. P. Nolan, *Org. Lett.* **1999**, *1*, 1307; b) S. R. Stauffer, S. Lee, J. P. Stambuli, S. I. Hauck, J. F. Hartwig, *Org. Lett.* **2000**, *2*, 1423.

[10] a) W. A. Herrmann, V. P. W. Böhm, C. W. K. Gstöttmayr, M. Grosche, C.-P. Reisinger, T. Weskamp, *J. Organomet. Chem.* **2001**, *616*, 617; b) C. Yang, S. P. Nolan, *Organometallics* **2002**, *21*, 1020.

[11] Very recently, it has been reported that $PdBr_2$(dmmdiy), having a bidentate imidazolol-2-ylidene ligand, could be used as a Pd(II) catalyst in silylstannation-cyclization of enynes; see Ref.[2i]

[12] For synthesis of **4f**, see: W. A. Herrmann, L. J. Goossen, C. Köcher, G. R. J. Artus, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2805.

[13] In the reaction using a chiral imidazolium salt **4f**, the cyclized product **2b** was obtained in 2% ee, which was determined from the ^1H NMR spectrum of the MPTA ester of **8b** after derivatization of **2b** by the procedure shown in Scheme 4.

[14] a) For synthesis of **5a**, see: F. Guillen, C. L. Winn, A. Alexakis, *Tetrahedron: Asymmetry* **2001**, *12*, 2083; b) for synthesis of **5b**, see: S. Lee, J. F. Hartwig, *J. Org. Chem.* **2001**, *66*, 3402; c) for synthesis of **5c**, see: T. J. Seiders, D. W. Ward, R. H. Grubbs, *Org. Lett.* **2001**, *3*, 3225; d) a novel imidazolinium salt **5d** was synthesized by the similar procedure reported in Ref.[14c]

[15] The cyclized products **2b** in the reaction using imidazolinium salts **5a** – **5d** were obtained with a low enantiomeric excess (e. g., **5a** 1% ee, **5b** 3% ee, **5c** 2% ee, **5d** 1% ee), which was also determined from the ^1H-NMR spectrum of the MPTA ester of **8b** derived from **2b**.

[16] The cyclized products **2a** in Table 4 were obtained with a low enantiomeric excess (e. g., **4f** not determined, **5a** 1% ee, **5b** 2% ee, **5c** 6% ee, **5d** 8% ee), which was determined from the ^1H-NMR spectrum of the MPTA ester of **8a** after derivatization of **2a** by the procedure shown in Scheme 3.