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Gold-Catalyzed 5- and 6-*exo-dig* Selective Cyclizations of Alkynyl Silyl Enol Ethers: Efficient Method for [3+2] and [4+2] Annulations onto α,β-Enones

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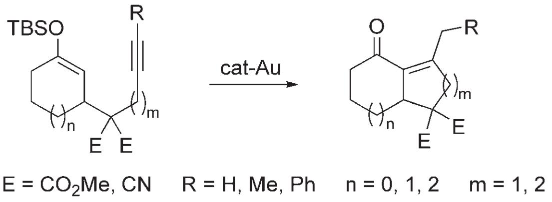
This paper is dedicated to the memory of Professor Moon Hwan Cho.

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

Abstract: An efficient method for the annulation of five- and six-membered rings onto α,β-enones is described *via* gold-catalyzed 5- and 6-*exo-dig* selective cyclizations of alkynyl silyl enol ethers.

Keywords: [3+2] annulation; [4+2] annulation; catalysis; cyclization; gold

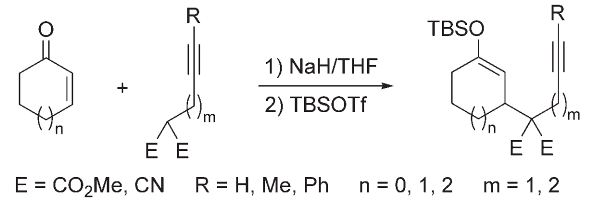
The development of novel methods for the annulation of five- and six-membered rings onto alkenes is very important in the field of synthetic organic chemistry because such methods enable a facile construction of the carbon frameworks found in natural products.[1] Although a variety of methods has been developed for this purpose, it is not easy to effectively achieve the annulation of a five- or six-membered ring onto α,β-enones. Danheiser et al. found a useful method for the [3+2] annulation of substituted trimethylsilylallenes and α,β-enones in the presence of an excess amount of $TiCl_4$.[2] Addition reactions of silyl enol ethers to alkynes were mediated by $EtAlCl_2$.[3] Recently, Iwasawa et al. reported a novel $W(CO)_5(L)$-catalyzed cyclization of ω-acetylenic silyl enol ethers,[4] where 5-siloxy-5-en-1-ynes undergo 6-*endo-dig* cyclization[4a,b] and 7-siloxy-6-en-1-ynes undergo either 5-*exo-dig* or 6-*endo-dig* cyclization by the appropriate choice of the reaction conditions.[4c] Moreover, Iwasawa and Lee et al. revealed that 6-siloxy-5-en-1-ynes and 6-siloxy-1,2,5-trienes undergo $W(CO)_5(L)$-catalyzed 5-*endo-dig* and 5-*endo-trig* cyclization to give β,γ-enones and γ,δ-enones in good to excellent yields, respectively.[5] Despite this recent progress, a variety of efficient synthetic annulation methods for a five- and six-membered ring is still needed to overcome problems related to the availability and ease of handling of the reagents, operational simplicity and selectivity. Also, various tungsten-mediated annulation methods are effective only for the cyclization of compounds having C/C multiple bond such as an alkynyl and allenyl group at the terminus.[4,5] As part of a project aimed at finding new cyclopentene and cyclohexene annulations that would be useful in organic synthesis, we report herein an efficient gold-catalyzed synthetic method for the annulation of five- and six-membered rings onto alkenes as a result of 5- and 6-*exo-dig* carbocyclizations of 7-siloxy-6-en-1-ynes and 8-siloxy-7-en-1-ynes, respectively (Scheme 1).[6]



Scheme 1. 5- or 6-*exo-dig* Selective cyclization catalyzed by Au.

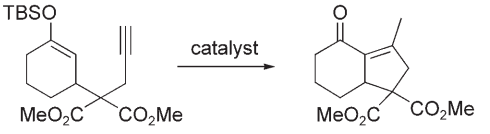
In the first place, various 7-siloxy-6-en-1-ynes or 8-siloxy-7-en-1-ynes were prepared from the 1,4-addition of propargyl or homopropargyl malonate to α,β-enones followed by *in situ* trapping of the intermediate enolate using *tert*-butyldimethylsilyl triflate in moderate to good yields (Scheme 2).

Next, the reaction conditions for the gold-catalyzed cyclization were examined employing 7-siloxy-6-en-1-yne **1c** as a substrate and the results are summarized in Table 1. 5 mol % AuCl gave the cyclopentene product **2c** in 65 % yield *via* 5-*exo-dig* cyclization followed



Scheme 2. 1,4-Adition of active methylene componuds having alkynyl group to α,β-enones.

Table 1. Optimization of the cyclization reactions of alkynyl silyl enol ethers.[a]



1c **2c**

Entry	Catalyst	Solvent	Time [min]	Temp [°C]	Yield [%][b]
1	AuCl	CH_2Cl_2	180	25	65(28)
2	$AuCl_3$	CH_2Cl_2	5	25	82(13)
3[c]	$AuCl_3$	CH_2Cl_2	180	25	48(44)
4[d]	$AuCl_3$	CH_2Cl_2	30	25	21(19)[e]
5	$AuCl_3$/AgOTf	DCE	120	80	72(20)
6	Ph_3PAuCl	DCE	11[f]	80	70
7[g]	Ph_3PAuCl/AgOTf	DCE	9[f]	80	91
8[g]	AgOTf	CH_2Cl_2	5	25	66(30)
9	AgOTf	CH_2Cl_2	5	25	50(44)

[a] 5 mol% AuCl, 5 mol% $AuCl_3$, 5 mol% Ph_3PAuCl and 15 mol% AgOTf were used.

[b] GC yield based on 2-methoxynaphthalene as an internal standard.

[c] 1 mol% $AuCl_3$ was used.

[d] Molecular sieve (3 Å) was added as an additive.

[e] Compound **1c** was recovered in 48% yield on GC.

[f] Hours.

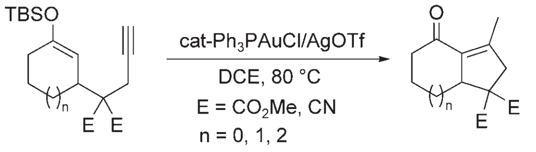
[g] 5 mol% AgOTf was used.

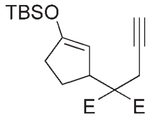
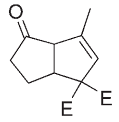
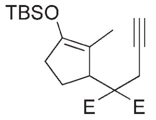
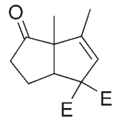
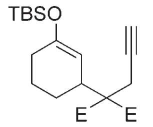
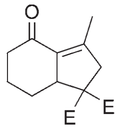
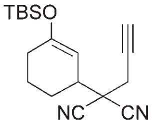
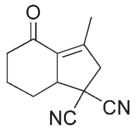
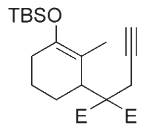
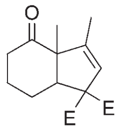
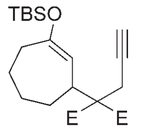
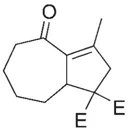
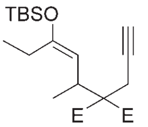
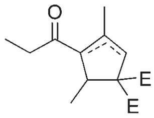
by isomerization together with the ketone produced by hydrolysis of **1c** in 28% yield (entry 1). In addition, 1 mol% $AuCl_3$ afforded **2c** and ketone in 48% and 44% yields, respectively (entry 3). Although the use of 5 mol% $AuCl_3$ increased the yield of **2c** (82%), hydrolysis of enol silyl ether before cyclization is inevitable (entry 2). Examination of temperature changes and a variety of solvents failed to suppress the formation of ketone with catalytic $AuCl_n$ ($n=1$ and 3). The use of molecular sieve as an additive did not improve the yield of **2c** and suppress the formation of ketone (entry 4). Compound **2c** was produced in 72% yield using 5 mol% $AuCl_3$ in the presence of 15 mol% AgOTf together with the ketone in 20% yield (entry 5). However, 5 mol% Ph_3PAuCl gave selectively the desired product **2c** in 70% yield (entry 6). No ketone compound was formed, indicating that the enol silyl ether is more easily desilylated in AuCl and $AuCl_3$ than in Ph_3PAuCl and the ketone might be produced by hydrolysis due to trace amounts of water in the reaction mixture. 5 mol% Ph_3PAuCl and 5 mol% AgOTf in DCE at 80°C for 9 h under a nitrogen atmosphere produced selectively α,β-enone **2c** in 91% yield *via* 5-*exo-dig* cylization followed by isomerization (entry 7). The use of 5 and 15 mol% AgOTf gave **2c** in 66% and 50% yield contaminated by ketone in 30% and 44% yields, respectively (entries 8 and 9). DCE was the best solvent among several reaction media (CH_2Cl_2, toluene, and benzene) that were examined. Although 5 mol% $AuCl_3$ gave **2c** in 82% yield at 25°C for 5 min, 5 mol% Ph_3PAuCl and 5 mol% AgOTf in DCE at 80°C was chosen as optimum conditions because ketone formation caused to hydrolysis of **1c** is avoidable.

To demonstrate the efficiency and scope of the present method, a variety of 7-siloxy-6-en-1-ynes were treated with 5 mol% Ph_3PAuCl and 5 mol% AgOTf. The results are summarized in Table 2. Under the optimum conditions, compound **1a** and **1b** were cyclized smoothly to give the desired products having double bond at β,γ-position *via* 5-*exo-dig* cylization followed by isomerization in 90% and 84% yields, respectively (entries 1 and 2). In case of silyl enol ether **1d** having a propargyl malonitrile, the desired product **2d** was obtained in 82% yield (entry 4). In addition, the silyl enol ether having a terminal alkynyl group obtained from 2-methyl-2-cyclohexen-1-one gave **2e** in 72% yield (entry 5). The yield of cyclization in **1b** and **1e** might be decreased due to steric hindrance of the methyl group at the α-position (entry 1 *vs.* 2 and entry 3 *vs.* 5). 7-Siloxy-6-en-1-yne (**1f**) derived from 2-cyclohepten-1-one and propargyl malonate gave rise to the bicyclo[5.3.0]decenone **2f** in 84% yield (entry 6). Exposure of the silyl enol ether derived from 4-hexen-3-one and propargyl malonate to optimum conditions furnished the cyclized product **2g** in 80% yield (α,β-enone:β,γ-enone = 7:1) *via* 5-*exo-dig* cylization (entry 7).

Encouraged by these results, silyl enol ethers derived from dimethyl malonate having an internal alkynyl group were treated with optimum conditions and the results are summarized in Table 3. Reaction of **1h** with 5 mol% Ph_3PAuCl and 5 mol% AgOTf in DCE gave **2h** in 45% yield *via* 5-*exo-dig* cyclization followed by isomerization together with the ketone compound in 38% yield at 90°C for 13 h (entry 1). 7-Siloxy-6-en-1-yne **1i** possessing a phenyl substituent at the terminal alkynyl group produced the [3+2] annulation product **2i** and ketone in 56% and 35% yields, respectively (entry 3). However, 10 mol% Ph_3PAuCl

Table 2. Gold-catalyzed 5-*exo-dig* cyclization of alkynyl silyl enol ethers having a terminal alkynyl group.[a]



Entry	Substrates	Products	Time [h]	Yield [%][b]
1	 **1a**	 **2a**	9	90
2	 **1b**	 **2b**	6	84
3	 **1c**	 **2c**	9	87
4	 **1d**	 **2d**	9	82
5	 **1e**	 **2e**	11	72
6	 **1f**	 **2f**	11	84
7	 **1g**	 **2g**	11	80[c]

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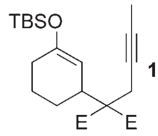
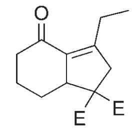
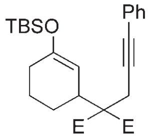
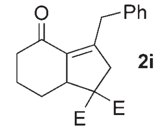
[a] 5 mol% Ph_3PAuCl and 5 mol% AgOTf were used. E = CO_2Me.

[b] Isolated yield.

[c] Ratio of α,β-enone and β,γ-enone = 7:1.

Table 3. Gold-catalyzed 5-*exo-dig* cyclization of alkynyl silyl enol ethers having an internal alkynyl group.[a]

Entry	Substrates	Products	Time [h]	Yield [%][b]
1	 **1h**	 **2h**	13	45 (38)
2[c]			13	62 (28)
3	 **1i**	 **2i**	12	56 (35)
4[c]			12	71 (24)

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[a] 5 mol% Ph_3PAuCl and 5 mol% AgOTf were used. E = CO_2Me.

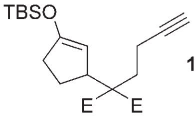
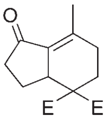
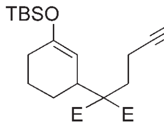
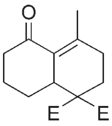
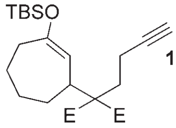
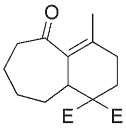
[b] Isolated yield. Numbers in parenthesis indicate the yield of ketone compound obtained from hydrolysis of silyl enol ether.

[c] 10 mol% Ph_3PAuCl and 10 mol% AgOTf were used.

and 10 mol% AgOTf increased the yields (62% and 71%) of **2h** and **2i**, respectively (entries 2 and 4). The cyclization of **1i** is more efficient than that of **1h** due to the generation of a more stable partial positive charge. Because cyclization of silyl enol ethers an having internal alkynyl group needed a longer reaction time than that for a terminal alkynyl group, yields of ketone compounds *via* hydrolysis of enol silyl ethers might be increased. It is noteworthy that silyl enol ethers having an internal alkynyl group were cyclized to give the desired product in good yield. This is contrast to the specific cyclization of alkynyl silyl enol ethers having terminal alkynes with catalytic amount of tungsten.

On the basis of above results, the [4+2] annulation of ω-alkynyl silyl enol ethers derived from 2-cycloalken-1-one and homopropargyl malonate was examined in detail (Table 4). Treatment of **1j** with 10 mol% Ph_3PAuCl and 10 mol% AgOTf afforded the bicyclic α,β-enone *via* 6-*exo-dig* cylization followed by isomer-

Table 4. Gold-catalyzed 6-*exo-dig* cyclization of alkynyl silyl enol ethers having a terminal alkynyl group.[a]

Entry	Substrates	Products	Time [h]	Yield [%][b]
1	 **1j**	 **2j**	2	83(12)
2	 **1k**	 **2k**	2	80(14)
3	 **1l**	 **2l**	2	84(11)

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[a] 10 mol% Ph_3PAuCl and 10 mol% AgOTf were used. E = CO_2Me.

[b] Isolated yield. Numbers in parenthesis indicate the yield of ketone compound obtained from hydrolysis of silyl enol ether.

ization and ketone compound *via* hydrolysis of silyl enol ether in 83% and 12% yields, respectively (entry 1). Reaction of **1k** with cat-gold under the optimum conditions gave the bicyclo[4.4.0]decenone in 80% yield (entry 2). 8-Siloxy-7-en-1-yne **1l** obtained from 2-cyclohepten-1-one and homopropargyl malonate gave rise to the bicyclo[5.4.0]undecenone in 84% yield (entry 3).

At present the reaction is assumed to proceed as follows: treatment of the silyl enol ether **1c** with 5 mol% Ph_3PAuCl and 5 mol% AgOTf generates the η^2-alkyne complexes **A** and/or the vinylidene complex **D**.[6] When this complex **A** is formed, the alkyne part becomes electron deficient due to the $[Au]^+$ and intramolecular attack of the silyl enol ether occurs to give the vinyl metallic intermediate **B**, which is finally protonated and isomerized to give the cyclopentene **2c** (Scheme 3). Because [4+2] annulation product *via* **E** from **1c** was not produced, the intermediate vinylidene complex **D** was excluded in this mechanism. To obtain information on the mechanism of this reaction, we have carried out D_2O experiments. After completion of cyclization of **1c** (80 °C, 9 h), addition of D_2O (15 equivs.) to the reaction mixture produced a compound[7] with deuterium incorporated in the methylene group at the α′-position instead of the compound with deuterium incorporated in the methyl group at the β-position, indicating that vinylgold **B** might abstract acidic protons at the α- and/or α′-position of intermediate **B**. Treatment of **1c** with cat-Ph_3PAuCl/AgOTf in the presence of D_2O (15 equivs.) gave the complicated results on TLC.

In conclusion, a novel gold-catalyzed synthetic method for the annulation of a five- or six-membered ring onto alkenes was developed as a result of the 5-*exo-dig* or 6-*exo-dig* carbocyclizations of 7-siloxy-6-en-1-ynes or 8-siloxy-7-en-1-ynes, respectively. It is noteworthy that sily enol ethers having internal alkynes as well as terminal alkynes were smoothly cyclized to give cyclopentene and cyclohexene annulation products in good to excellent yields. The present method complements the existing synthetic methods due to some advantages such as availability and easy of handling of reagents, operational simplicity, and high selectivity. These results should immediately provide more opportunities for the elucidation of efficient new cyclopentene and cyclohexene annulation strategies.

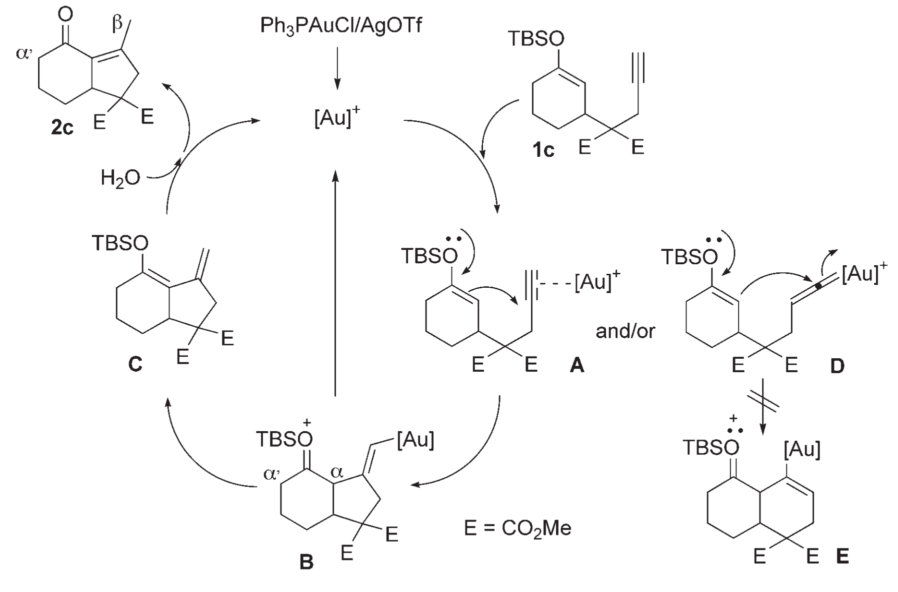
Experimental Section

General Remarks

Reactions were carried out in oven-dried glassware under a nitrogen atmosphere. All commercial reagents were used without purification, and all solvents were reaction grade. THF was freshly distilled from sodium/benzophenone under a nitrogen. DCE was freshly distilled from calcium hydride under a nitrogen. All reaction mixtures were stirred magnetically and were monitored by thin-layer chromatography using Merck silica gel 60 F_{254} precoated glass plates, which were visualized with UV light, and then, developed by using Fluka silica gel 60 (0.040–0.063 mm, 230–400 mesh). Commercially available solvents were purified by standard procedures.

Preparation of Dimethyl 3-*tert*-Butyldimethylsilyl-2-cyclohexen-1-yl propargylmalonate (1c)

To a suspension of NaH (60%, 76.8 mg, 1.92 mmol) in THF (5 mL) was added dimethyl propargylmalonate (219.5 mg,



Scheme 3. Proposed pathway for the cyclization of siloxy enynes.

1.29 mmol) at 0 °C under a nitrogen atmosphere. After 30 min, 2-cyclohexen-1-one (96.1 mg, 1.0 mmol) and TBSOTf (301.4 mg, 1.14 mmol) were added at room temperature. After 2 h, the reaction mixture was quenched with buffer solution (pH 7, $KH_2PO_4+Na_2HPO_4$). The aqueous layer was extracted with EtOAc (3×20 mL). The combined organics were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 20:1) to give the desired product; yield: 304.0 mg (80 %).

Typical Procedure for Cyclization of 7-Siloxy-6-en-1-ynes or 8-Siloxy-6-en-1-ynes

To a suspension of Ph_3PAuCl (11.1 mg, 0.0223 mmol) and AgOTf (5.7 mg 0.0223 mmol) in DCE (1.3 mL) was added 7-siloxy-6-en-1-yne or 8-siloxy-6-en-1-yne (0.45 mmol) in DCE (1 mL) at room temperature under a nitrogen atmosphere. After being stirred at 80 °C for 9 h, the reaction mixture was cooled at room temperature. The reaction mixture was diluted with CH_2Cl_2 (5 mL), filtered through Celite and then the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 3:1) to give the desired product.

Supporting Information

Characterization data for the products are available in the Supporting Information.

Acknowledgements

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References

[1] a) M. Ramaiah, *Synthesis* **1984**, 529; b) B. M. Trost, *Angew. Chem. Int. Ed.* **1986**, *25*, 1; c) M. T. Crimmins, E. A. Tabet, *J. Org. Chem.* **2001**, *66*, 4012; d) D. B. England, T. D. O. Kuss, R. G. Keddy, M. A. Kerr, *J. Org. Chem.* **2001**, *66*, 4704; e) H. M. L. Davies, B. Xiang, N. Kong, D. G. Stafford, *J. Am. Chem. Soc.* **2001**, *123*, 7461; f) J. Barluenga, S. Martínez, A. L. Suárez-Sobrino, M. Tomás, *J. Am. Chem. Soc.* **2002**, *124*, 5948; g) P. Ding, L. Ghosez, *Tetrahedron* **2002**, *58*, 1565; h) F. Mahuteau-Betzer, L. Ghosez, *Tetrahedron* **2002**, *58*, 6991; i) J. E. Wilson, G. C. Fu, *Angew. Chem. Int. Ed.* **2006**, *45*, 1426.

[2] a) R. L. Danheiser, D. J. Carini, A. Basak, *J. Am. Chem. Soc.* **1981**, *103*, 1604; b) R. L. Danheiser, D. J. Carini, D. M. Fink, A. Basak, *Tetrahedron* **1983**, *39*, 935; c) R. L. Danheiser, D. M. Fink, Y.-M. Tsai, *Org. Synth.* **1988**, *66*, 8; d) S. J. Panek, in: *Comprehensive Organic Synthesis*, (Ed.: B. M. Trost), Pergamon Press, Oxford, **1991**, Vol. 1, pp 596.

[3] a) K. Imamura, E. Yoshikawa, V. Gevorgyan, Y. Yammamoto, *Tetrahderon Lett.* **1999**, *40*, 4081; b) K. Imamura, E. Yoshikawa, V. Gevorgyan, T. Sudo, N. Asao, Y. Yamamoto, *Can. J. Chem.* **2001**, *79*, 1624.

[4] a) K. Maeyama, N. Iwasawa, *J. Am. Chem. Soc.* **1998**, *120*, 1928; b) N. Iwasawa, K. Maeyama, H. Kusama, *Org. Lett.* **2001**, *3*, 3871; c) T. Miura, N. Iwasawa, *Org. Lett.* **2002**, *4*, 2569.

[5] a) N. Iwasawa, T. Miura, K. Kiyota, H. Kusama, K. Lee, P. H. Lee, *Org. Lett.* **2002**, *4*, 4463; b) T. Miura, K. Kiyota, H. Kusama, K. Lee, H. S. Kim, S. Kim, P. H. Lee, N. Iwasawa, *Org. Lett.* **2003**, *5*, 1725.

[6] a) G. Dyker, *Angew. Chem. Int. Ed.* **2000**, *39*, 4273; b) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553; c) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; d) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537; e) E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem. Int. Ed.* **2002**, *41*, 23; f) N. Asao, K. Takahashi, S. Lee, T. Kasahara, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 12650; g) A. S. K. Hashmi, *Gold Bull.* **2003**, *36*, 3; h) A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431; i) C. He, Z. Shi, *J. Org. Chem.* **2004**, *69*, 3669; j) X. Yao, C. Li, *J. Am. Chem. Soc.* **2004**, *126*, 6884; k) V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654; l) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164; m) N. Morita, N. Krause, *Angew. Chem. Int. Ed.* **2006**, *45*, 1987; n) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064; *Angew. Chem. Int. Ed.* **2006**, 45, 7896; o) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180.

[7] Deuterium incorporation: