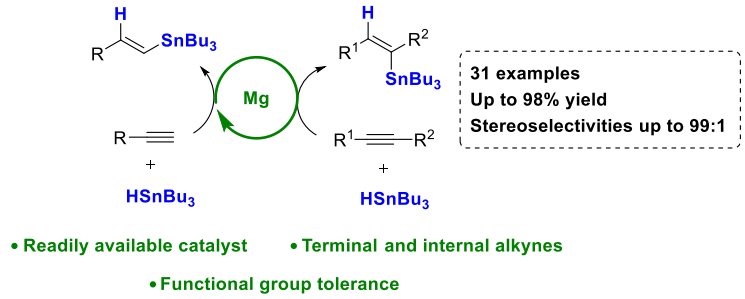
Magnesium Catalyzed Stereoselective Hydrostannylation of Internal and Terminal Alkynes

Marc Magre,[†] Marcin Szewczyk,[†] and Magnus Rueping*[,†,‡]

[†]Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany

[‡]KAUST Catalysis Center (KCC), King Abdullah University of Science and Technology (KAUST), Thuwal 23955-6900, Saudi Arabia



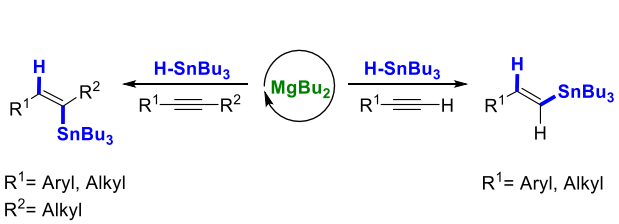
ABSTRACT: A regio- and stereoselective magnesium catalyzed hydrostannylation of internal and terminal alkynes has been developed. Excellent yields and selectivities are obtained for a wide range of terminal and internal symmetrical and unsymmetrical alkynes by using this alkaline earth metal catalyst as effective alternative to transition metal catalysts.

KEYWORDS: magnesium, alkynes, hydrostannylation, alkaline base earth-abundant metal

Organostannes are important organometallic reagents in organic synthesis due to their versatile transformations including C-C cross-coupling reaction.[1] Thus, the development of efficient methods for the preparation of organostannes has attracted considerable attention.[1] Despite the challenge of selectivity control, the hydrostannylation of alkynes[2] is one of the most efficient and economic routes to vinyl stannanes which are relevant synthetic intermediates in organic synthesis. Regarding their stereoselective synthesis, radical type hydrostannylations,[3] strong Lewis acid mediated[4] as well as transition metal catalyzed protocols have been developed to provide (*Z*)- or (*E*)-vinyl stannanes, respectively. Examples for the latter are Pd, Mo or Cu-catalyzed syn-addition which may require laborious and/or bulky ligands to achieve good regio- and stereoselectivities.[5-6] Nevertheless, these transition-metal catalyzed protocols paved the way for achieving hydrofunctionalizations of unsaturated bonds.

Alkaline and in particular alkaline earth metal based catalysts have attracted increasing attention in recent years as an alternative to transition metal catalysts.[7] Whereas more reactive Ca^{II}, Sr^{II}, and Ba^{II} catalysts have been widely applied,[7] the use of Mg^{II} catalysts has been mostly focused on hydroboration of unsaturated bonds.[8-10] In this respect and based on our interest in the further development of magnesium catalysis as an alternative to late transition metal catalysis, we decided to explore a magnesium catalyzed hydrostannylation of internal and terminal alkynes (Scheme 1).

We began our investigations of the magnesium catalyzed hydrostannylation using a symmetrical internal alkyne **1a** in the presence of readily available $MgBu_2$ (Table 1).

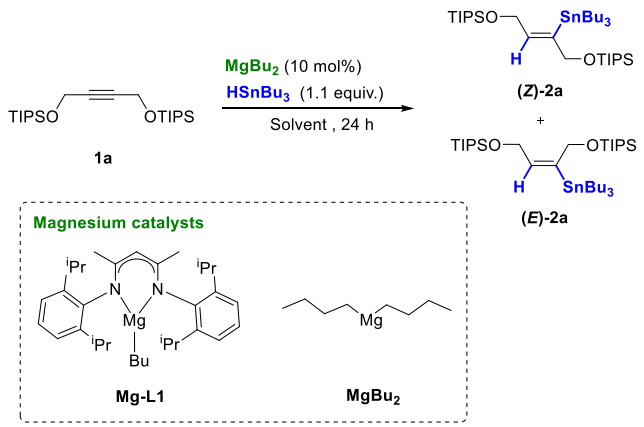


Scheme 1. $MgBu_2$-catalyzed hydrostannylation of terminal and internal alkynes.

$MgBu_2$ showed to be active at relatively mild reaction temperature (Table 1, entry 1), providing excellent yields and stereoselectivities towards product (*Z*)-**2a**. The change of reaction solvent resulted in lower yields and

toluene was established as the optimal solvent (Table 1, entries 2-3). By decreasing the temperature or the catalyst loading, we found out that $MgBu_2$ catalytic system is less active, but the excellent stereoselectivities were maintained (Table 1, entries 4 and 5). When we tested **Mg-L1** as catalyst (Table 1 entry 6), it turned out to show similar activity and selectivity than readily available MgBu2. Although the β-diketiminate Mg complex could also be used we decided to proceed with amine ligand-free $MgBu_2$ as catalyst as it is as easy to handle but allows a faster and simpler purification after the reaction.

Table 1. Optimization of $MgBu_2$-catalyzed hydrostannylation of alkyne 1a.[a]



entry	solvent	temp. (°C)	selectivity[b] (Z)-**2a** : (*E*)-**2a**	yield (%)[c]
1	toluene	50	>95:5	>99 (98)
2	THF	50	>95:5	92
3	CH_2Cl_2	50	n.d.	>5
4	toluene	23	>95:5	90
5[d]	toluene	50	>95:5	91
6[e]	toluene	50	>95:5	>99
7[f]	toluene	50	n.d.	>5

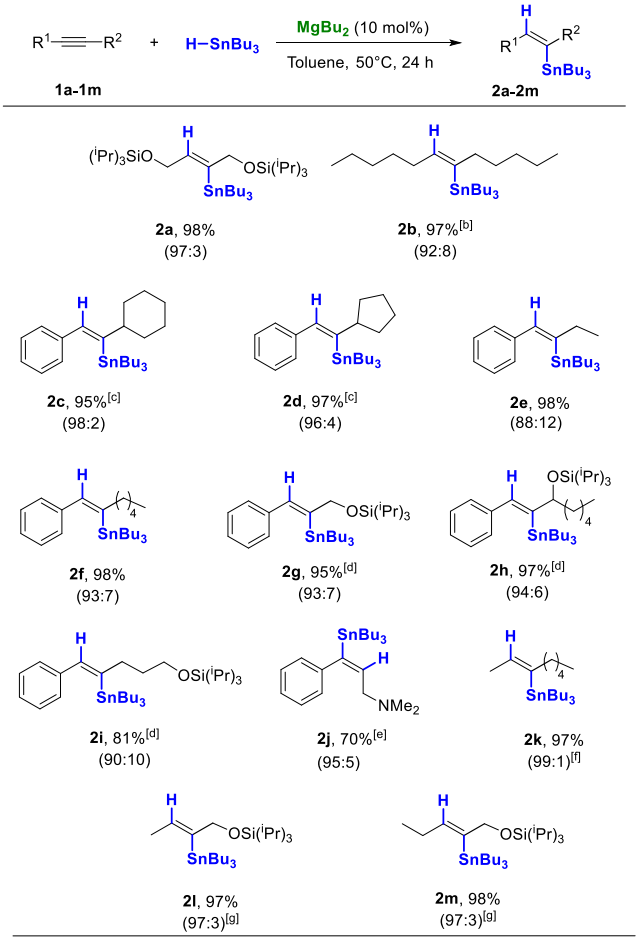
[a] $MgBu_2$ (1 M in heptane, 10 mol%), alkyne (**1a**, 1.0 mmol), 1.1 equiv. of $HSnBu_3$, solvent (1.5 mL, 0.7 M), for 24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. Isolated yields in parenthesis. [d] 5 mol% of $MgBu_2$ were used. [e] Using **Mg-L1** (10 mol%) as catalyst. [f] No catalyst was used.

With the optimized reaction conditions, we explored the scope and limitations of the $MgBu_2$-catalyzed hydrostannylation of different internal alkynes (Scheme 2).

For both symmetrical internal alkynes **1a** and **1b**, the major stereoisomer obtained was (*Z*)-**2a** and (*Z*)-**2b**, respectively. We could observe that the presence of *O*-protected groups on the alkyl substituent did not influence the stereochemistry of the product. Subsequently, we tested more challenging unsymmetrical alkynes **1c-1m**, which are known to cause problems of regioselectivity.[5-6] We were delighted to see that $MgBu_2$ catalyst can successfully catalyze the hydrostannylation of internal aryl-alkyl alkynes (**1c-1f**), not only stereoselectively but also regioselectively, achieving in all cases the β-(*Z*)- isomer. Depending on the size of the alkyl substituent, the stereoselectivity slightly varies while maintaining the excellent levels of regioselectivity.

We were pleased to see that the presence of *O*-protected groups on the alkyl chain (**1g-1i**) did not have an influence on either activities or selectivities, achieving in all cases excellent yields and regio- and stereoselectivities. Surprisingly, when the internal alkyne bearing an *N*-protected group (**1j**) was tested, opposite regio- and stereoselectivities were achieved, affording the corresponding α-(*E*)-**2j**. We attribute this behavior to the stronger coordinative effect of the NMe_2-group compared to the bulky OTIPS-group. The good catalytic performance of $MgBu_2$ for the hydrostannation of internal aryl-alkyl alkynes was further extended to internal alkyl-alkyl alkynes **1k-1m**, achieving excellent yields and stereoselectivities. Similar to the hydrostannation of symmetrical internal alkynes (**1a-1b**), the major stereoisomer for the unsymmetrical internal alkynes (**1c-1i**, **1k-1m**) was found to be (*Z*)-vinyl stanne, indicating that the hydrostannation occurs in a *trans*-fashion.[11]

Scheme 2. $MgBu_2$-catalyzed hydrostannylation of internal alkynes.[a]



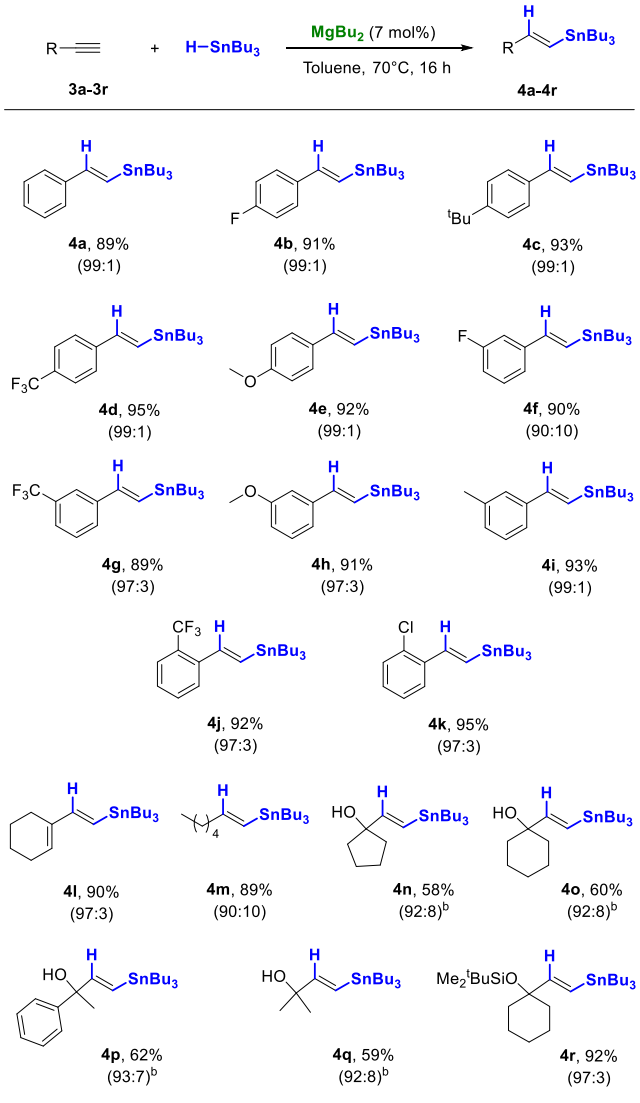
[a] Reaction conditions: **1a-1m** (1.0 mmol), 1.1 mmol. $HSnBu_3$, $MgBu_2$ (10 mol%), toluene (1.5 mL), 50 °C for 24 h. Yields after purification. [b] Neat, 23 °C, 72 h. [c] 48 h. [d] 23 °C, 24 h. [e] ^{1}H NMR yield. [f] 40% of β-regioisomer. [g] 7% of

β-regioisomer. For detailed information, see Supporting Information.

Finally, in order to expand the substrate scope, we tested several terminal alkynes (Scheme 3). When applying the same conditions to the terminal alkyne **3a** we observed poor stereoselectivity towards (*E*)-**4a**.[12] We could solve this selectivity problem by increasing the temperature (for details, see Supporting Information) while maintaining the excellent yields and regioselectivities.

With the optimized reaction conditions, we investigated the scope and limitations of our catalytic system. First, we tested various phenylacetylene derivatives with different electronic properties (**3a-3e**) and we were pleased to see that there was no influence on the catalytic activity, achieving in all cases excellent yields and regio- and stereoselectivities towards β-(*E*)-vinyl stannes **4a-4e**.

Scheme 3. $MgBu_2$-catalyzed hydrostannylation of internal alkynes.[a]



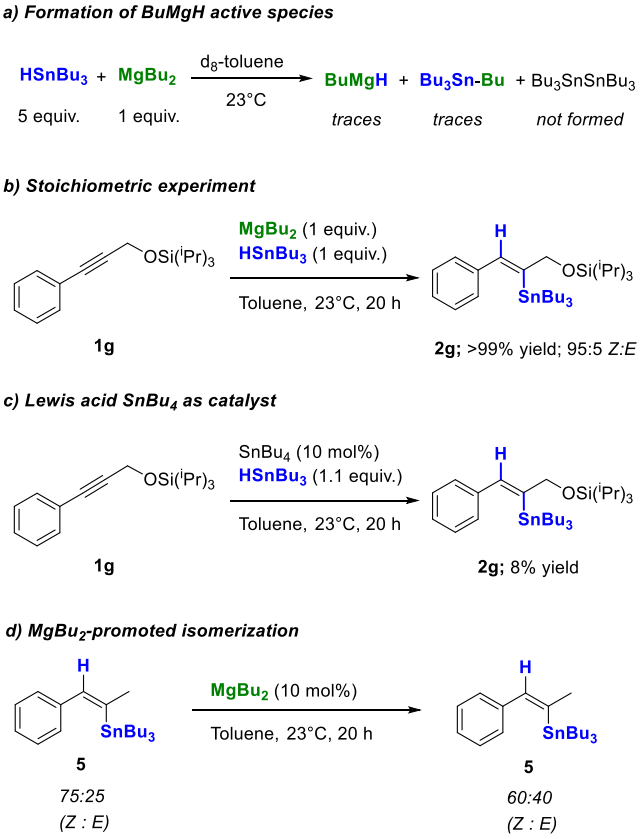
[a] Reaction conditions: **3a-3r** (1.0 mmol), 1.1 mmol. $HSnBu_3$, $MgBu_2$ (7 mol%), toluene (1.5 mL), 70 °C for 16 h. Yields after purification. Selectivities are referred to β-(*E*)-**4** *versus* other regio- and stereoisomer (α-**4** and β-(*Z*)-**4**). For detailed information, see Supporting Information. [b] Mg-L1 was used.

Remarkably, these excellent selectivities are superior to those obtained using transition-metal catalysts, for which the regioselectivities showed to be electronically dependent.[5c-5d] Moreover, this good performance was also observed for sterically differentiated phenylacetylene derivatives **4f-4k**.

Regarding terminal aliphatic alkynes, we observed that our $MgBu_2$ catalytic system is able to hydrostannylate terminal alkynes containing cyclic (**4l**), and linear (**4m**) alkyl substituents with excellent regio- and stereoselectivities, competing favorably with the best reports in the literature.[5-6]

Propargylic alcohols **3n-3q** were also tested. However, $MgBu_2$ was not able to provide the corresponding β-(*E*)-vinyl stanne with acceptable regioselectivity.[13-14] To solve this regioselectivity problem, sterically hindered **Mg-L1** catalyst was now used in order to diminish the ability of the hydroxyl moiety as a directing group.[13] We were delighted to see that vinylstannes **4n-4q** could now be isolated in excellent regio- and stereoselectivities, albeit in moderate-to-good yields. Finally, we studied *O*-protected propargylic alcohol **3r**. In contrast to its respective unprotected alkynol (**4o**), excellent yields and regioselectivities were obtained with $MaBu_2$.

Scheme 4. Control experiments.



Previous reports have shown that the $MgBu_2$-catalyzed hydroboration of terminal and internal alkynes proceed through a BuMgH active species, which undergoes hydromagnesiation of alkynes in a *syn*-fashion and, follow-

ing Mg/B exchange, (*E*)-vinyl borane products are achieved. Herein we report that for the $MgBu_2$-catalyzed hydrostannylation of alkynes the stereochemical outcome is, however, opposite.

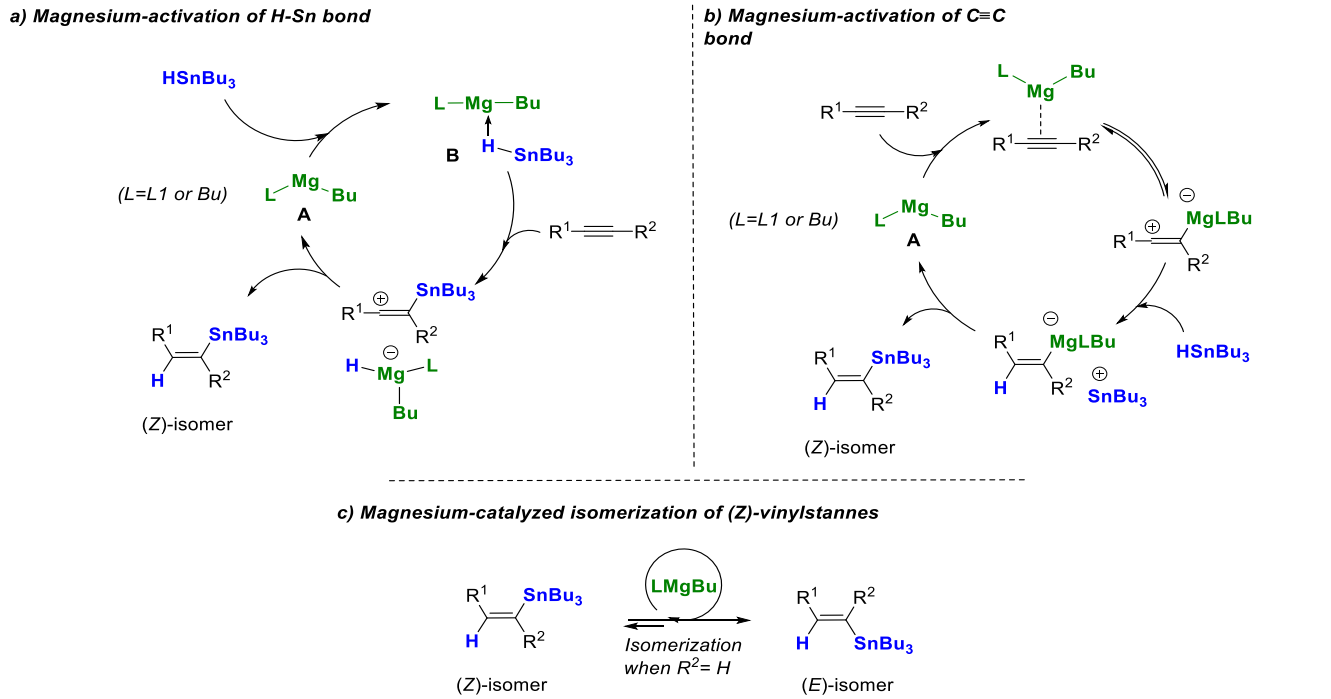
In order to get more information on the reaction mechanism, we decided to perform several control experiments (Scheme 4). First, due to the *trans*-stereoselectivity observed, we confirmed our hypothesis that the $MgBu_2$-catalyzed hydrostannylation of alkynes does not take place through active species BuMgH. When $MgBu_2$ was mixed with stoichiometric excess of $HSnBu_3$ (Scheme 4a), only traces of $SnBu_4$ were observed (for details, see Supporting Information). This finding agrees with the different hydride reactivity that HBpin and $HSnBu_3$ present. Whereas hydridic B-H bond undergoes σ-bond metathesis with $MgBu_2$ to provide active species BuMgH, Sn-H bond does not.[15] We also conducted stoichiometric experiments (Scheme 4b) and observed that only one molecule of $HSnBu_3$ is necessary to obtain the corresponding vinylstanne product in quantitative yield. This result discards the possibility of a mechanism that involves the formation of active BuMgH species, therefore $MgBu_2$ activates $HSnBu_3$ through a different pathway.[16] Given that traces of $SnBu_4$ were formed when catalyst and tri-*n*-butyltin hydride were mixed, we tested if Lewis acidic $SnBu_4$ could potentially catalyze the transformation (Scheme 4c). In this case, only traces of product **2g** could be observed, discarding the possibility that Lewis acidic $SnBu_4$ acts as a catalyst. By additional control experiments (Scheme 4d), we have proven that $MgBu_2$ is able to isomerize (*Z*)- vinylstannes to (*E*)-vinylstannes. Depending on the size of the R^2 substituent, the isomerization is more favored, which explains the isomerization observed when terminal alkynes were studied.

In agreement with Weiner and Still *et al.*[17] who reported that organotin/organolithium exchange occurs in equilibrium, we believe that organomagnesium can also undergo exchange with the vinylstanne, providing the more thermodynamically stable (*E*)-stereoisomer.

Regarding the mechanism and catalytic cycle of the $MgBu_2$-catalyzed hydrostannylation of alkynes we can only postulate that it may be similar to those reported using strong Lewis acids and the recently reported *trans*-hydrophosphination reaction.[18] In line with all experimental data we propose that the stereoselective *trans*-hydrostannylation takes place through a carbocationic intermediate in which either the stannane or alkyne is activated by the Mg-catalyst (Scheme 5a, b). Moreover, we have observed that (*Z*)-vinylstannes (Scheme 4d and Supporting Information) isomerize to more thermodynamically stable (*E*)-products in the presence of $MgBu_2$. Although there is no relevant data in the literature which support this isomerization, our findings led us to propose that Mg-catalyst isomerizes vinylstanne species *via* carbanion species, as Mitchell and coworkers reported when vinylstannes are mixed with organolithium species.[19, 17]

In summary, we report the first active and selective catalytic system based on inexpensive and readily available magnesium catalyst for the hydrostannylation of terminal and internal alkynes. Under relatively mild reaction conditions and low catalysts loadings, excellent yields and regio- and stereoselectivities have been achieved for a wide range of terminal and internal alkynes, even for challenging unsymmetrical substrates. Moreover, mechanistic studies suggest that hydrostannylation may occur through Lewis acidic activation either of $HSnBu_3$ or C≡C bond, providing the corresponding vinylstannes. Finally, we have proven that $MgBu_2$ can also isomerize (*Z*)-vinylstannes to more stable (*E*)-stereoisomer.

Scheme 5. Proposed mechanisms for $MgBu_2$-catalyzed hydrostannylation of alkynes (Scheme 5a and b). $MgBu_2$-catalyzed isomerization of vinylstannes (Scheme 5c).



ASSOCIATED CONTENT

The Supporting Information is available free of charge on the

ACS Publications website.
Experimental procedures, characterization and NMR spectra (PDF).

AUTHOR INFORMATION

Corresponding Author

* Magnus Rueping : magnus.rueping@rwth-aachen.de

Notes

The authors declare no competing financial interest.

REFERENCES

[1] a) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508–524. b) Peyrere, M.; Quintard, J. P.; Rahm, A. Tin in Organic Synthesis, Butterworth: London, **1987**. c) Espinet, P.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734. d) Fürstner, A.; Funel, J. A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. *Chem. Commun.* **2008**, 2873–2875.

[2] For recent reviews on hydrostannylation of alkynes, see: a) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257–3282. b) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853–887. c) Yoshida, H. *Synthesis* **2016**, *48*, 2540–2552. d) Alami, M.; Hamze, A.; Provot, O. *ACS Catal.* **2019**, *9*, 3437–3466.

[3] For selected examples on radical hydrostannation, see: a) Oderinde, M. S.; Froese, R. D. J.; Organ, M. G. *Angew. Chem. Int. Ed.* **2013**, *52*, 11334–11338. b) Gupta, S.; Do, Y.; Lee, J. H.; Han, J.; Rhee, Y. H.; Park, J. *Chem. Eur. J.* **2014**, *20*, 1267–1271.

[4] For examples of Lewis acid-catalyzed hydrostannylation of alkynes, see: a) Asao, N.; Liu, J.-X.; Sudoh, T.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 2405–2046. b) Asao, N.; Liu, J.-X.; Sudoh, T.; Yamamoto, Y. *J. Org. Chem.* **1996**, *61*, 4568–4571. c) Gevorgyan, V.; Liu, J.-X.; Yamamoto, Y. *Chem. Commun.* **1998**, 37–38. For *trans*-hydrostannation catalyzed by trityl cation, see: d) Forster, F.; Rendón López, V. M.; Oestreich, M. *Organometallics* **2018**, *37*, 2656–2659.

[5] For selected examples using transition-metal catalysts, see: a) Ichinose, Y.; Oda, H.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3468–3470. b) Darwish, A.; Lang, A.; Kim, T.; Chong, J. M. *Org. Lett.* **2008**, *10*, 861–864. c) Mandla, K. A.; Moore, C. E.; Rheingold, A. L.; Figueroa, J. S. *Angew. Chem. Int. Ed.* **2018**, *57*, 6853–6857. d) Cheng, L.-J.; Mankad, N. P. Heterobimetallic *J. Am. Chem. Soc.* **2019**, *141*, 3710–3716.

[6] For Ru-catalyzed *trans*-hydrofunctionalization, see: a) Rummelt, S. M.; Fürstner, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 3626–3630. b) Rummelt, S. M.; Radkowski, R.; Rosca, D.-A.; Fürstner, A. *J. Am. Chem. Soc.* **2015**, *137*, 5506–5519. c) Rosca, D.-A.; Radkowski, K.; Wolf, L. M.; Wagh, M.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2017**, *139*, 2443–2455.

[7] For recent reviews on the use of alkaline-base earth abundant metals as catalysts, see: a) Crimmin, M. R.; Hill, M. S. *Top. Organomet. Chem.* **2013**, *45*, 191–241. b) Revunova, K.; Nikonov, G. I. *Dalton Trans.* **2015**, *44*, 840–866. c) Hill, M. S.; Liptrot, D. J.; Weetman, C. *Chem. Soc. Rev.* **2016**, *45*, 972–988. d) Pellissier, H. *Org. Biomol. Chem.* **2017**, *15*, 4750–4782.

[8] Examples on magnesium hydroboration of unsaturated bonds, see: a) Arrowsmith, M.; Hadlington, T. J.; Hill, M. S.; Kociok-Köhn, G. *Chem. Commun.* **2012**, *48*, 4567–4569. b) Arrowsmith, M.; Hill, M. S.; Kociok-Köhn, G. *Chem. Eur. J.* **2013**, *19*, 2776–2783. c) Mukherjee, D.; Ellern, A.; Sadow, A. D. *Chem. Sci.* **2014**, *5*, 959–964. d) Fohlmeister, L.; Stasch, A. *Chem. Eur. J.* **2016**, *22*, 10235–10246. e) Mukherjee, D.; Shirase, S.; Spaniol, T. P.; Mashima, K.; Okuda, J. *Chem. Commun.* **2016**, *52*, 13155–13158. f) Manna, K.; Ji, P.; Greene, F. X.; Lin, W. *J. Am. Chem. Soc.* **2016**, *138*, 7488–7491. g) Rauch, M.; Ruccolo, S.; Parkin, G. *J. Am. Chem. Soc.* **2017**, *139*, 13264–13267. h) Li, J.; Luo, M.; Sheng, X.; Hua, H.; Yao, W.; Pullarkat, S. A.; Xu, L.; Ma, M. *Org. Chem. Front.* **2018**, *5*, 3538–3547. i) Falconnet, A.; Magre, M.; Maity, B.; Cavallo, L.; Rueping, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 17567–17571.

[9] For the use of readily available Mg-catalysis, see: a) Magre, M.; Bholanath, M.; Falconnet, A.; Cavallo, L.; Rueping, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 7025–7029. b) Jang, Y. K.; Magre, M.; Rueping, M. *Org. Lett.* **2019**, *21*, 8349–8352. c) Szewczyk, M.; Magre, M.; Zubar, V.; Rueping, M. *ACS Catal.* **2019**, *9*, 11634–11639. d) Chatupheeraphata, A.; Magre, M.; Rueping, M. *Org. Lett.* **2019**, *21*, 9153-9157.

[10] Leading examples for the use of β-diketiminate magnesium complexes in C–H and C–F activations: a) Davin, L.; McLellan, R.; Kennedy, A. R.; Hevia, E. *Chem. Commun.* **2017**, *53*, 11650–11653. b) Davin, L.; McLellan, R.; Hernán-Gómez, A.; Clegg, W.; Kennedy, A. R.; Mertens, M.; Stepek, I.; Hevia, E. *Chem. Commun.* **2017**, *53*, 3653-3656.

[11] Using transition-metal as catalyst (ref. 5), the major stereoisomer obtained for internal alkynes was the (*E*)-vinyl stanne. Füstner and coworkers (ref. 6) have recently reported the Ru-catalyzed *trans*-hydrostannylation of internal alkynes, providing the corresponding (*Z*)-vinyl stanne.

[12] The stereoselectivity of vinylstanne **2a** (50°C, 24 h) is >95:5 *Z*:*E* whereas the stereoselectivity of vinylstanne **4a** (50°C, 24 h) is 15:85 *Z*:*E*.

[13] For selected examples on the regiochemical influence of directing groups on the alkynes, see: a) Zhang, H. X.; Guibe, F.; Balavoine, G.; *J. Org. Chem.* **1990**, 55, 1857–1867. b) Rice, M. B.; Whitehead, S. L.; Horvath, C. M.; Muchnij, J. A.; Maleczka, R. E. *Synthesis* **2001**, *10*, 1495–1504.

[14] Using $MgBu_2$ as catalyst, vinylstanne **4q**, was isolated as a mixture of β-(*E*)-**4q** and α-**4q** in a 80:20 ratio.

[15] Whereas HBpin provides the corresponding TM–H, H–GeR_3 and H–SnR_3 provide the corresponding TM–Ge or TM–Sn species. a) Sharma, S.; Oehlschlager. A. C. *J. Org. Chem.* **1989**, *54*, 5064–5073. b) Comanescu, C. C.; Iluc, V. M. *Chem. Commun.* **2016**, *52*, 9048–9051.

[16] Regarding the use of stoichiometric Mg-Sn species, Cummins and co-workers reported that $Bu_3SnMgMe$ species are able to react with diphenylacetylene providing the corresponding *trans*-stannylmagnesiate product: a) Cummins, C. H.; Gordon, E. J. *Tetrahedron Lett.* **1994**, 35, 8133–8136. In this respect, Baba and coworkers reported the use of [$Bu_2SnIBrH$][MgBr] tin hydride ate complex for the selective α-hydrostannylation of terminal alkynes, b) Shibata, I.; Suwa, T.; Ryu, K.; Baba, A. *J. Am. Chem. Soc.* **2001**, *123*, 4101–4102.

[17] For organotin/organolithium exchange equilibrium, see: a) Seyferth, D.; Weiner, M. A. *J. Am. Chem. Soc.* **1962**, *84*, 361–364. b) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487.

[18] Pahl, J.; Stennett, T. E.; Volland, M.; Guldi, D. M.; Harder, S. *Chem. Eur. J.* **2019**, *25*, 2025–2034.

[19] Mitchell, T. N.; Reimann, W. *J. Organomet. Chem.* **1985**, *19*, 163–171.