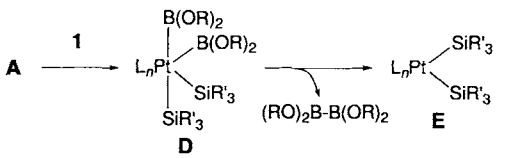
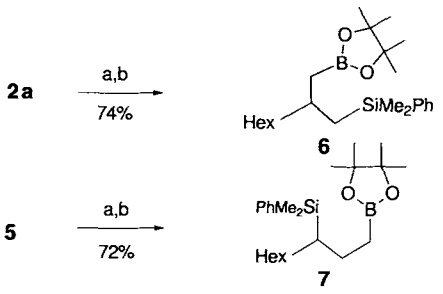
oxidative addition of **1** to the Pt^0 complex,[10] followed by reductive elimination of diborane (Scheme 4). Formation of **D** could be suppressed by using $[Pt(PPh_3)_4]$ as a catalyst, that is, in the presence of excess PPh_3.



Scheme 4. Possible route of formation of a bis(silyl)platinum complex.

The silaboration reaction made possible a regioselective C–C bond formation at the boryl-substituted C atom. For example, one-carbon homologation of **2a** and **5**, prepared from 1-octene and 1-octyne, respectively, was carried out (Scheme 5). Treatment of **2a** and **5** with chloro(trimethylsilyl)methyllithium gave the corresponding homologation products **6** and **7**, respectively, after selective removal of the trimethylsilyl group by tetrabutylammonium fluoride (TBAF).[11]



Scheme 5. Synthesis of **6** and **7**: a) Me_3SiCH_2Cl, *s*BuLi, *N,N,N',N'*-tetramethyl ethylene diamine, THF, −78 °C b) TBAF, THF, reflux.

Here we have presented preliminary results on the regioselective silaboration of simple alkenes. Optimization of the reaction conditions on the basis of the mechanism shown in Scheme 3 is currently underway.

Experimental Section

General procedure for silaboration of alkenes: To a solution of platinum catalyst (0.076 mmol) in dioxane (1 mL) were added silylborane **1** (3.9 mmol) and alkene (5.9 mmol). The mixture was heated at reflux for 2 h. Evaporation of volatile materials under reduced pressure was followed by column chromatography on silica gel to give **2** and **3** in the yields listed in Tables 1 and 2.

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[1] a) T. Ishiyama, N. Matsuda, N. Miyaura, A. Suzuki, *J. Am. Chem. Soc.* **1993**, *115*, 11018–11019; b) T. Ishiyama, N. Matsuda, M. Murata, F. Ozawa, A. Suzuki, N. Miyaura, *Organometallics* **1996**, *15*, 713–720.

[2] a) H. Okinoshima, K. Yamamoto, M. Kumada, *J. Organomet. Chem.* **1975**, *96*, C27–C30; b) H. Sakurai, Y. Kamiyama, Y. Nakadaira, *J. Am. Chem. Soc.* **1975**, *97*, 931–932; c) Y. Ito, M. Suginome, M. Murakami, *J. Org. Chem.* **1991**, *56*, 1948–1951; d) H. Yamashita, M. Catellani, M. Tanaka, *Chem. Lett.* **1991**, 241–244; e) F. Ozawa, M. Sugawara, T. Hayashi, *Organometallics* **1994**, *13*, 3237–3243; f) for a review on palladium-catalyzed bis-silylation, see K. A. Horn, *Chem. Rev.* **1995**, *95*, 1317–1350.

[3] T. N. Mitchell, K. Kwetkat, D. Rutschow, U. Schneider, *Tetrahedron* **1989**, *45*, 969–978.

[4] M. Suginome, H. Nakamura, Y. Ito, *Chem. Commun.* **1996**, 2777–2778.

[5] S. Onozawa, Y. Hatanaka, T. Sakakura, S. Shimada, M. Tanaka, *Organometallics* **1996**, *15*, 5450–5452.

[6] a) T. N. Mitchell, H. Killing, R. Dicke, R. Wickenkamp, *J. Chem. Soc. Chem. Commun.* **1985**, 354–355; b) B. L. Chenard, C. M. V. Zyl, *J. Org. Chem.* **1986**, *51*, 3561–3566; c) M. Murakami, H. Amii, N. Takizawa, Y. Ito, *Organometallics* **1993**, *12*, 4223–4227.

[7] a) R. T. Baker, P. Nguyen, T. B. Marder, S. A. Westcott, *Angew. Chem.* **1995**, *107*, 1451–1452; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1336–1337; b) T. Ishiyama, M. Yamamoto, N. Miyaura, *Chem. Commun.* **1997**, 689–690.

[8] a) T. Hayashi, T. Kobayashi, A. M. Kawamoto, H. Yamashita, M. Tanaka, *Organometallics* **1990**, *9*, 280–281; b) M. Murakami, P. G. Andersson, M. Suginome, Y. Ito, *J. Am. Chem. Soc.* **1991**, *113*, 3987–3988; c) M. Murakami, M. Suginome, K. Fujimoto, H. Nakamura, P. G. Andersson, Y. Ito, *ibid.* **1993**, *115*, 6487–6498; d) M. Suginome, Y. Yamamoto, K. Fujii, Y. Ito, *ibid.* **1995**, *117*, 9608–9609; e) M. Suginome, A. Matsumoto, Y. Ito, *ibid.* **1996**, *118*, 3061–3062.

[9] The reaction of (E)-$CH_3(CH_2)_5CH{=}CHB(OR)_2$, prepared independently by hydroboration, with $PhMe_2SiH$ in the presence of $[Pt(CH_2{=}CH_2)(PPh_3)_2]$ (2 mol%) at 110 °C for 10 h gave **3a** selectively, albeit in low yield (ca. 10%).

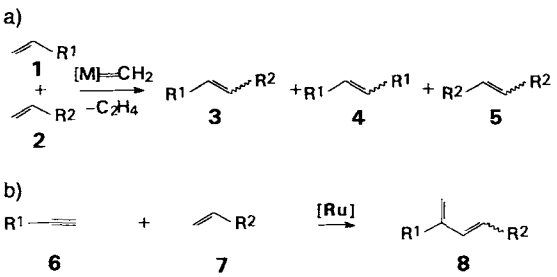
[10] M. Suginome, H. Oike, P. H. Shuff, Y. Ito, *J. Organomet. Chem.* **1996**, *521*, 405–408.

[11] D. S. Matteson, D. Majumdar, *Organometallics* **1983**, *2*, 230–236; D. J. S. Tsai, D. S. Matteson, *ibid.* **1983**, *2*, 236–241.

A Crossed Yne–Ene Metathesis Showing Atom Economy**

Roland Stragies, Matthias Schuster, and Siegfried Blechert*

Transition metal catalyzed olefin metathesis has recently acquired increasing significance in organic chemistry.[1] Ring-closing metatheses (RCM) have been shown especially reliable for the preparation of five- through eight-membered rings and larger systems.[2] Applications of RCM to the synthesis of fluvirucine,[3] epothilone,[4] and other natural products[5] verify the efficiency of this approach to carbon–carbon bond formation. To date, olefin metathesis has primarily been employed in organic chemistry as a synthetic method for cyclization. There are far fewer examples of the synthesis of acyclic alkenes by selective cross-metathesis of two different alkenes. In the cross-metathesis of two terminal alkenes **1** and **2** one must of necessity take into account the formation of homodimers **4** and **5** (Scheme 1a). Based on early results it is nonetheless possible to carry out highly selective couplings by the choice of suitable substituents.[6] To our knowledge, nothing has previously been



Scheme 1. a) Cross-metathesis of two terminal alkenes; b) crossed yne–ene metathesis.

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reported with respect to the corresponding behavior of terminal alkynes. We describe here examples of atom economy[7] in selective cross couplings of monosubstituted alkynes with alkenes. Metatheses of alkynes are above all known from polymerizations and a few ring-closing metatheses. Thus, cyclizations of enynes to five- through seven-membered rings have been reported.[8a] This reaction principle found an elegant application in the synthesis of stemoamide.[8b] A double ring-closing metathesis to bicyclic systems has also been achieved by treatment of appropriate dienynes.[9] However, much more common than such intramolecular reactions is the intermolecular metathesis of alkynes, leading to polymers. Apart from the polymerization of simple alkynes,[10] the ring-closing metathesis polymerization of 1,6-heptadiynes has proven especially interesting.[11]

In the course of systematic studies on selective cross-metathesis we found that terminal alkynes **6** and terminal alkenes **7** were transformed selectively by ruthenium catalysis into disubstituted dienes **8** (Scheme 1b). In contrast to the cross-metathesis of two alkenes, no ethylene or other by-product is released in this case; that is, C–C bond formation occurs with atom economy. To date, catalysis of this reaction has been successful only with the Grubbs ruthenium catalyst[12] $[Cl_2(PCy_3)_2Ru{=}CHPh]$(**[Ru]**; Cy = cyclohexyl). Use of the more reactive Schrock molybdenum catalyst[13] $[PhMe_2CCH{=}Mo{=}N(2,6\text{-}iPr_2C_6H_3)\{OCMe(CF_3)_2\}_2]$ has polymerization of the alkyne component[9] as its only consequence under the same reaction conditions. Figure 1 illustrates several products of the new cross-metathesis process.[14] The reaction is carried out in dichloromethane at room temperature with 5–7 mol% **[Ru]**.

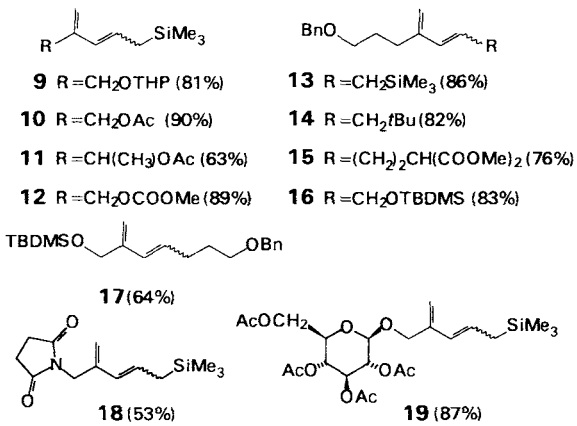
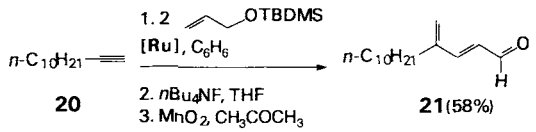


Figure 1. Products of the ruthenium-catalyzed crossed yne–ene metathesis. THP = tetrahydro-2*H*-pyran-2-yl, TBDMS = *tert*-butyldimethylsilyl.

Reported yields were achieved within 12–48 h using a two- to threefold excess of the alkene component; a greater excess leads to no increase in yield. With a 1:1 mixture one does indeed obtain dienes as the main products, but in lower yield. Dimerization of the alkenes occurs only to a very limited extent.

Because of the great synthetic potential of allylsilanes, we undertook initial experiments in the reaction of allyltrimethylsilane with alkynes. Once the alkene had been coupled with THP-protected propargyl alcohol highly selectively and in acceptable yield to give the 1,3-disubstituted diene **9**, we also examined the behavior of propargyl acetate and carbonate. Compounds **10**–**12** show that coupling occurs smoothly here as well. The resulting allyl acetate structural unit offers diverse possibilities for subsequent reactions. Allylic acetates as well as the usually more reactive allylic carbonates are of interest, for example, in π-allylpalladium chemistry.[15] Due to the combination of an allylsilane with an allylic acetate or carbonate, **10**–**12** can be regarded as vinylogous trimethylenemethane precursors.[16] We are currently investigating their Pd-catalyzed reactions. The facile, selective cross-coupling reactions with allylsilanes cannot be attributed to special electronic characteristics of this particular class of compounds: comparison of **13** and **14** shows that the carbon analogue of allyltrimethylsilane, 4,4-dimethyl-1-pentene, reacts in similarly high yield. Coupling product **15** from benzyl-protected 4-pentyne-1-ol and dimethyl (3-butenyl)-malonate demonstrates the applicability of strongly CH-acidic alkenes. However, no reaction occurs with the corresponding dimethyl allylmalonate, presumably due to steric effects.

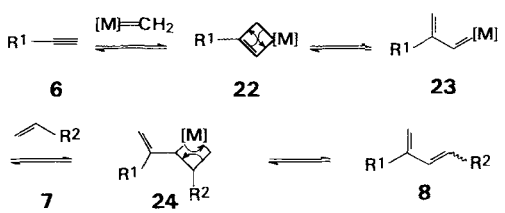
The coupling of a TBDMS-protected allylic alcohol with an alkyne to give **16** is just as successful as the inverse combination of alkene and alkyne to **17**. It is apparent from the syntheses of **18** and **19** that nitrogen-containing and highly functionalized substrates are also applicable. Yields were considerably poorer with unprotected alcohols. Disubstituted alkynes or 1,2-substituted alkenes fail to react under the conditions employed. Coupling products **9**–**19** arise as isomeric mixtures; the (*Z*)/(*E*) ratios as determined by ^{1}H NMR spectroscopy lie in a range between 1:3 in the case of **11** and about 1:2 to 1:1 with the other compounds. Because of this lack of stereoselectivity we are currently investigating techniques for (*Z*)/(*E*) isomerization. One possibility is presented in Scheme 2 with the synthesis of α-triticene[17] (**21**), an antifungal compound isolated from cereal



Scheme 2. Synthesis of α-triticene (**21**).

seeds. Because of the higher solubility of alkyne **20** this metathesis was carried out in benzene. The metathesis product was deprotected in a one-pot reaction and oxidized directly with MnO_2, in the course of which it was isomerized completely to the desired (*E*)-isomer, isolated in an overall yield of 58%.

Metallacyclobutenes are assumed to be intermediates in the reaction of alkynes with metathesis catalysts.[9, 11] Several mechanisms are possible for the ruthenium-catalyzed yne–ene metathesis. NMR studies have shown that the ruthenium catalyst reacts selectively with alkynes in the presence of alkenes. In the absence of alkene there occurs only a slow oligomerization, whereas in its presence a rapid subsequent reaction leads to product **8**. We therefore favor the reaction course illustrated in Scheme 3. We assume as the first step that the methylidene complex formed from the Grubbs catalyst undergoes a regioselective [2+2] cycloaddition with the triple bond of **6**. Subsequent cycloreversion leads to the stabilized, conjugated carbene complex **23**. This reacts through further [2+2] cycloaddition with alkene



Scheme 3. Proposed mechanism for the yne–ene metathesis.

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component **7** to give **24**, and with subsequent cycloreversion to the conjugated diene **8**. The fact that coupling is limited to terminal alkynes may have a steric origin. Formation of the more stable and thus less reactive conjugated carbene complex **23** might explain why the yne–ene metathesis requires longer reaction times than conventional cross-metathesis between alkenes. Volatile ethylene is formed in the cross-metathesis of terminal alkenes, whereas the yne–ene metathesis takes place with atom economy. The driving force in yne–ene metathesis may be the formation of a conjugated diene.

The type of reaction described here is, to our knowledge, the first selective crossed yne–ene metathesis. Application of this cross-metathesis between terminal alkynes and alkenes has been demonstrated by the synthesis of variously functionalized dienes. The reaction opens the way to interesting structural elements: thus, conjugated allylsilanes have found a variety of applications, for example in Sakurai reactions.[18] The metathesis products are also of interest with respect to Diels–Alder reactions and cycloadditions. We are currently investigating the applications of yne–ene metathesis in natural product synthesis.

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[1] Regarding olefin metathesis in organic synthesis: a) A. S. K. Hashmi, *J. Prakt. Chem.* **1997**, *339*, 195; b) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem. Int. Ed. Engl.* **1997**, *35*, 2036.

[2] Reviews on ring-closing metathesis: a) H. G. Schmalz, *Angew. Chem.* **1995**, *107*, 1981; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1833; b) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446; selected recent examples of ring-closing metathesis: c) C. M. Huwe, S. Blechert, *Synthesis* **1997**, 61; d) A. B. Dyatkin, *Tetrahedron Lett.* **1997**, *38*, 2065; e) D. Meng, D.-S. Su, A. Balog, P. Bertinato, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *J. Am. Chem. Soc.* **1997**, *119*, 2733; f) K. Hammer, K. Undheim, *Tetrahedron* **1997**, *53*, 2309.

[3] A. F. Houri, Z. M. Xu, D. A. Cogan, A. H. Hoveyda, *J. Am. Chem. Soc.* **1995**, *117*, 2943.

[4] Z. Yang, Y. He, D. Vourloumis, H. Vallberg, K. C. Nicolaou, *Angew. Chem.* **1997**, *109*, 170; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 166; D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm, M. Cordes, *ibid.* **1997**, *109*, 543 and **1997**, *36*, 523.

[5] a) A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 8746; b) A. Fürstner, N. Kindler, *Tetrahedron Lett.* **1996**, *37*, 7005; c) S. Hölder, S. Blechert, *Synlett* **1996**, 505; d) H. S. Overkleeft, U. K. Pandit, *Tetrahedron Lett.* **1996**, *37*, 547.

[6] Examples of cross-metatheses: a) O. Brümmer, A. Rückert, S. Blechert, *Chem. Eur. J.* **1997**, *3*, 441; b) J. Feng, M. Schuster, S. Blechert, *Synlett* **1997**, 129; c) A. G. M. Barrett, S. P. D. Baugh, V. C. Gibson, M. R. Giles, E. L. Marshall, P. A. Procopiou, *Chem. Commun.* **1997**, 155; d) W. E. Crowe, D. R. Goldberg, Z. J. Zhang, *Tetrahedron Lett.* **1996**, *37*, 2117; e) A. G. M. Barrett, J. C. Beall, V. C. Gibson, M. R. Giles, G. L. P. Walker, *Chem. Commun.* **1996**, 2229; f) W. E. Crowe, D. R. Goldberg, *J. Am. Chem. Soc.* **1995**, *117*, 5162; g) W. E. Crowe, Z. J. Zhang, *ibid.* **1993**, *115*, 10998; h) E. S. Finkelshtein, N. V. Ushakov, E. B. Portnykh, *J. Mol. Catal.* **1992**, *76*, 133.

[7] B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.

[8] a) A. Kinoshita, M. Mori, *Synlett* **1994**, 1020; b) *J. Org. Chem.* **1996**, *61*, 8356.

[9] S.-H. Kim, N. B. Bowden, R. H. Grubbs, *J. Am. Chem. Soc.* **1994**, *116*, 10801.

[10] a) R. Schlund, R. R. Schrock, W. E. Crowe, *J. Am. Chem. Soc.* **1989**, *111*, 8004; b) T. Masuda, T. Higashimura, *Acc. Chem. Res.* **1984**, *17*, 51.

[11] a) J. W. Park, J. H. Lee, H. N. Cho, S. K. Choi, *Macromolecules* **1993**, *26*, 1191; b) Review on metathesis polymerization: R. R. Schrock, *Pure Appl. Chem.* **1994**, *66*, 1447.

[12] P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem.* **1995**, *107*, 2179; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039.

[13] R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875.

[14] Representative experimental procedure for yne–ene cross-metathesis: propargyl acetate (280 mg, 2.85 mmol) and allyltrimethylsilane (980 mg, 8.57 mmol) were dissolved in dichloromethane (15 mL). After addition of **[Ru]** (165 mg, 0.19 mmol) the mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated under vacuum and purified chromatographically with *tert*-butyl methyl ether/petroleum ether (1/9) on silica gel. There was obtained 543 mg (90%) of product **10**. (*E*)/(*Z*)-isomers were assigned on the basis of ^{1}H-^{1}H and ^{1}H-^{13}CNMR correlation measurements (400 MHz). Selected spectroscopic data: (E)-**10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (d, J = 16 Hz, 1H), 5.7 (dd, J = 16 Hz, 8 Hz, 1H), 5.03 (s, 1H), 5.00 (s, 1H), 4.70 (s, 2H), 2.07 (s, 3H), 1.54 (d, J = 8 Hz, 2H), −0.02 (s, 9H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 170.5 (C), 140.1 (C), 128.5 (CH), 127.3 (CH), 113.8 (CH_2), 64.1 (CH_2), 23.6 (CH_2), 20.7 (CH_3), −1.95 (CH_3); (*Z*)-**10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65 (d, J = 13 Hz, 1H), 5.63 (dd, J = 13 Hz, 8 Hz, 1H), 5.22 (d, J = 2 Hz, 1H), 5.10 (s, 1H), 4.66 (s, 2H), 2.07 (s, 3H), 1.73 (d, J = 8 Hz, 2H), 0.04 (s, 9H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 170.4 (C), 139.8 (C), 130.4 (CH), 123.7 (CH), 114.5 (CH_2), 66.8 (CH_2), 20.7 (CH_3), 20.0 (CH_2), −2.2 (CH_3); MS: *m/z*(%): 212 (5) [M^+], 197 (3), 169 (5) [$M^+ - C_2H_3O$], 117 (25), 79 (100), 73 (91), 43 (18); HR-MS: calcd for $C_{11}H_{20}O_2Si$ [M^+]: 212.1233, found: 212.122.

[15] J. Tsuji, *Tetrahedron* **1986**, *42*, 4361.

[16] a) B. M. Trost, *Angew. Chem.* **1986**, *98*, 1; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1; b) *Pure Appl. Chem.* **1988**, *60*, 1615.

[17] P. J. Spendley, P. M. Bird, J. P. Ride, D. P. Leworthy, *Phytochemistry* **1982**, *21*, 2403.

[18] D. Seyferth, J. Pornet, R. M. Weinstein, *Organometallics* **1982**, *12*, 1651.

Total Synthesis of Eleutherobin**

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Eleutherobin[1, 2] **1** (Figure 1) is a newly discovered antitumor agent which has a mechanism of action[3] like Taxol (**2**) and a novel molecular architecture. Its structure was based on spectroscopic results,[1, 2] although no absolute configuration was assigned. Isolated from an *Eleutherobia* species of marine soft corals (possibly *E. albiflora* Alcynacea, Alcyoniidea) collected in the Indian Ocean near Bennett's Shoal in Western Australia, this substance is extremely scarce, and yet its tubulin polymerization and microtubule-stabilizing properties and 100-fold higher potency (over the mean cytotoxicity of an NIH cell line panel) against selected breast, renal, ovarian, and lung cancer cells[2] make it (along with epothilones[4–9] A (**3**) and B (**4**), Figure 1), one of the most promising antitumor agents isolated from nature in recent years. Here we report the first total synthesis of eleutherobin (**1**) which renders the natural product (**1**) and two biologically active analogues (**33** and **34**, see Scheme 3) readily available for further studies. Furthermore, the described chemical synthesis allows assignment of the absolute stereochemistry of eleutherobin (**1**) and opens an avenue for the generation of combinatorial libraries for biological screening purposes.

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