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Efficient and Stereoselective Synthesis of Yellow Scale Pheromone via Alkyne Haloboration, Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA Reaction), and Pd-Catalyzed Tandem Negishi Coupling

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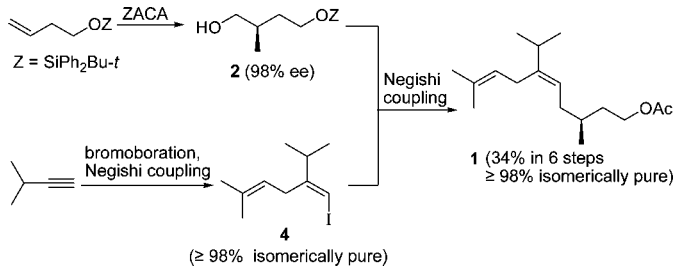
ABSTRACT



A Pd-catalyzed reaction of allylzincs with the 1-octyne bromoboration product gives the desired allyl−alkenyl coupling products in good yields except with $H_2C{=}CHCH_2ZnBr$. This reaction is suitable for converting an alkyne bromoboration product 3 into 4 with no isomerization or β-elimination. The Pd-catalyzed isoalkyl−alkenyl coupling of 4 with the isoalkylzinc reagent derived from 2 provides yellow scale pheromone (1) of ≥98% isomeric purity in 34% in six steps from TBDPS-protected homoallyl alcohol.

Hydrometalation and carbometalation of alkynes followed by Pd-catalyzed cross-coupling[1] have provided a variety of highly stereoselective and efficient routes to di- and trisubstituted alkenes.[2] Even so, however, there still are a large number of trisubstituted alkenes that are not readily preparable by these methods, as exemplified by the sex pheromone of yellow scale (**1**),[3] a pest of citrus and ornamental plants. It was isolated and identified without the establishment of full stereochemical details by Gieselmann and his co-workers

(1) For seminal contributions, see: (a) Negishi, E.; Baba, S. *J. Chem. Soc., Chem. Commun.* **1976**, *596*, 597. (b) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729–6731. (c) Negishi, E.; Van Horn, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 3168–3170. (d) Okukado, N.; Van Horn, D. E.; Klima, W. L.; Negishi, E. *Tetrahedron Lett.* **1978**, *1027*, 1030. (e) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254–2256. (f) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahetron Lett.* **1979**, *3437*, 3440.

(2) For recent reviews, see: (a) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002; p 3279; Chapters III.2.6, III.2.9, III.2.11, III.2.15. (b) de Meijere, A., Diederich, F., Eds. *Metal-catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004; 916 pp. (c) Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichim. Acta* **2005**, *38*, 71–88. (d) Negishi, E.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.*, in press.

(3) (a) Gieselmann, M. J.; Moreno, D. S.; Fargerleund, J.; Tashiro, H.; Roelofs, W. L. *J. Chem. Ecol.* **1979**, *5*, 25–31. (b) Anderson, R. J.; Henrick, C. A. *J. Chem. Ecol.* **1979**, *5*, 773–779. (c) Suguro, T.; Roelofs, W. L.; Mori, K. *Agric. Biol. Chem.* **1981**, *45*, 2509–2514. (d) Masuda, S.; Kuwahara, S.; Suguro, T.; Mori, K. *Agric. Biol. Chem.* **1981**, *45*, 2515–2520. (e) Mori, K.; Kuwahara, S. *Tetrahedron* **1982**, *38*, 521–525. (f) Millar, J. G. *Tetrahedron Lett.* **1989**, *30*, 4913–4914.

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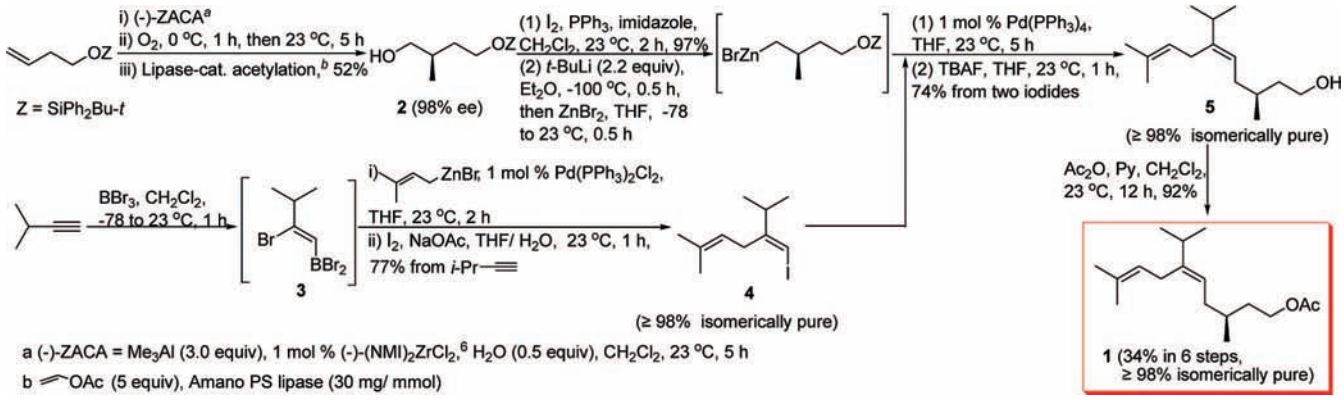
Scheme 1. Regio- and Stereoselective Synthesis of Yellow Scale Pheromone



in 1979.[3a] In the same year, the active isomer of **1** was shown to be the 5*E* isomer by a deliberate synthesis of a mixture of the 5*E* and 5*Z* isomers by Anderson and Henrick.[3b] Mori and his co-workers subsequently established the 3*S* configuration of the active isomer through asymmetric syntheses of both enantiomers.[3d,e] Although highly stereoselective, their syntheses based on the chiral pool protocol suffered from a lengthy sequence of over 10 steps from methyl (*R*)-(+)-citronellate in 7−10% overall yields. A very promising, convergent, but nonasymmetric route to **1** via silylcupration[4] was devised more recently by Millar.[3f]

The synthetically challenging trisubstituted alkene moiety of **1** and an opportunity for applying the ZACA reaction (Zr-catalyzed asymmetric carboalumination of alkenes),[5] especially one-pot synthesis of (2*S*)-4-*tert*-butyldiphenylsilyloxy-2-methyl-1-butanol (**2**) of 98% ee in 52% yield from TBDPS-protected 3-buten-1-ol,[5d] prompted us to devise an efficient and regio- and stereoselective synthesis of **1**, as outlined in Scheme 1.

For construction of the trisubstituted alkene moiety, application of alkyne haloboration developed by Suzuki[7] was considered, and stereoselective formation of **3** in ca. 80% yield by the reaction of 3-methyl-1-butyne with BBr_3 in CH_2Cl_2 was observed. This was to be followed by selective and high-yielding cross-coupling. The high propensity of the bromoboration products, such as **3**, to undergo unwanted dehaloboration together with the modest reactivity of hindered alkenyl bromide would make desired C−C bond formation via cross-coupling of **3** challenging. In fact, the only known satisfactory cross-coupling appeared to be the Pd-catalyzed organozinc reaction[2] employed by Suzuki.[7] It then occurred to us that, whereas the Pd-catalyzed alkenylmetal−allyl electrophile (alkenyl−allyl, hereafter) coupling had been extensively investigated, generally high-yielding, and often highly regio- and stereospecific with retention with respect to both alkenyl and allyl groups,[8] little had been known about the corresponding allylmetal−alkenyl electrophile (allyl−alkenyl, hereafter) coupling.[8b] Since the Pd-catalyzed alkenyl−allyl coupling was not a viable option for the task at hand, however, the Pd-catalyzed allyl−alkenyl coupling of (*Z*)-(2-bromo-1-octenyl)dibromoborane, generated by treating 1-octyne with BBr_3 in CH_2Cl_2, with allylzinc bromide and its variously carbon-substituted derivatives generated by treating the corresponding allylic bromides with Zn dust was examined.[9] The results summarized in Table 1 indicate the following: (1) The Pd-catalyzed allyl−alkenyl coupling with the parent allylzinc bromide does not occur under the conditions used, but all of the other cases including those involving 2-methylallylzinc bromide gave the desired products in good yields. The sterically least demanding parent allylzinc bromide may act as a catalyst poison, although this point needs to be further investigated. (2) As anticipated, the Pd-catalyzed allyl−alkenyl coupling is more readily prone to stereoisomerization. Thus, the allylic organozinc reagents derived from both geranyl and neryl bromides led to the formation of essentially identical mixtures of the 4*E* and 4*Z* isomers (*E*/*Z* = 2.5/1) without producing detectable amounts of regioisomers. These results are in sharp contrast with the corresponding Pd-catalyzed alkenyl−allyl coupling proceeding with essentially complete retention of both stereo- and regiochemical identities.[8] Despite these limitations, the desired case of the conversion of **3** to **4** via Pd-catalyzed cross-coupling of **3** with 3-methyl-2-butenylzinc bromide in the presence of 1 mol % of $Pd(PPh_3)_2Cl_2$ followed by iodinolysis with I_2 (2 equiv) and NaOAc (1.5 equiv) proceeded cleanly with no detectable sign of isomerization to give **4** (≥98% *E*) in 77% yield from 3-methyl-1-butyne.

(4) For a seminal paper on silylcupration, see: Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, *252*, 7–2532.

(5) For seminal and pertinent papers on the ZACA reaction, see: (a) Kondakov, D.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 10771–10772. (b) Kondakov, D.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577–1578. (c) Huo, S.; Shi, J.; Negishi, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2141–2143. (d) Huang, Z.; Tan, Z.; Novak, T.; Zhu, G.; Negishi, E. *Adv. Synth. Catal.* **2007**, *349*, 539–545.

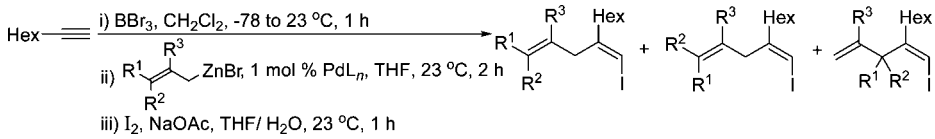
(6) Erker, G.; Aulbach, M.; Knickmeier, M.; Wingbermuhle, D.; Kruger, C.; Nolte, M.; Werner, S. *J. Am. Chem. Soc.* **1993**, *115*, 4590.

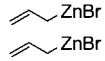
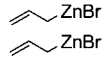
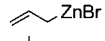
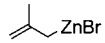
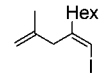
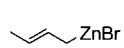
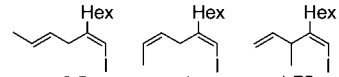
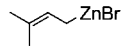
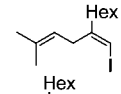
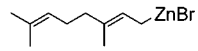
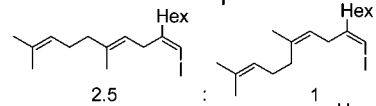
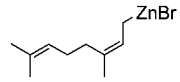
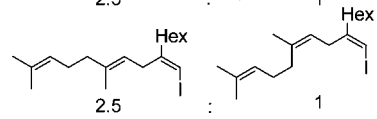
(7) (a) Satoh, Y.; Serizawa, H.; Miyaura, N.; Hara, S.; Suzuzki, A. *Tetrahedron Lett.* **1988**, *29*, 1811–1814. (b) For a seminal report on alkyne haloboration, see: Lappert, M. F.; Prokai, B. *J. Organomet. Chem.* **1964**, *1*, 384–400.

(8) (a) Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 2882–2884. (b) For a review, see: Negishi, E.; Liu, F. Chapter III.2.9 in ref 2a.

(9) (a) Shriner, R. L.; Neumann, F. W. *Organic Synthesis*; Wiley: New York, 1955; Vol. III, p 73. (b) Negishi, E.; Matsushita, H.; Okukado, N. *Tetrahedron Lett.* **1981**, *22*, 2715–2718.

Table 1. Scope of a Tandem Process Consisting of Alkyne Haloboration−Pd-Catalyzed Negishi Coupling with Allylzinc Bromide[a]



Entry	PdL_n	$R^1(R^2)(R^3)C{-}ZnBr$	Product	Yield[b] (%)
1	$Pd(PPh_3)_2Cl_2$		[c]	0
2	$Pd(DPEphos)Cl_2$		[c]	0
3	$Pd(t\text{-}Bu_3P)_2$		[c]	0
4	$Pd(PPh_3)_2Cl_2$			66
5	$Pd(PPh_3)_2Cl_2$		 3.5 : 1 : 1.75	69
6	$Pd(PPh_3)_2Cl_2$			83
7	$Pd(PPh_3)_2Cl_2$		 2.5 : 1	75
8	$Pd(PPh_3)_2Cl_2$		 2.5 : 1	81

[a] All reactions were run with 1.0 equiv of BBr_3, 1.2 equiv of allylzinc bromide generated by treating the corresponding allylic bromides with Zn dust, 2.0 equiv of I_2, and 1.5 equiv of NaOAc. [b] All yields refer to isolated yields. [c] No allyl−alkenyl coupling product was observable by GC and ^1H NMR.

For the final assembly of the full carbon skeleton of the yellow scale pheromone (**1**), **2** was iodinated in 97% yield by its treatment with I_2 (1.2 equiv), PPh_3 (1.15 equiv), and imidazole (1.3 equiv) in CH_2Cl_2. The iodide thus obtained was treated with *t*-BuLi (2.2 equiv) in ether[10] followed by zincation with dry $ZnBr_2$. The Pd-catalyzed isoalkyl−alkenyl coupling of the in situ generated isoalkylzinc reagent with **4** in the presence of 1 mol % of $Pd(PPh_3)_4$ followed by desilylation with TBAF (1.2 equiv), provided **5** as *a* ≥98% pure compound in 74% yield from the two iodide precursors,[11] and its acetylation gave the desired yellow scale pheromone (**1**) of ≥98% isomeric purity in 92% yield. Thus, **1** was synthesized in 34% yield over six steps in the longest linear sequence from TBDPS-protected 3-buten-1-ol or in 54% yield over four steps from 3-methyl-1-butyne.

In summary, the following notable findings have been discovered in this work. (1) The hitherto essentially unexplored Pd-catalyzed allylzinc−alkenyl electrophile coupling has been investigated. The parent allylzinc bromide does not give the desired allyl−alkenyl coupling products under the conditions used. Fortunately, all of the other allylzinc derivatives with one or two substituents in the C2 or C3 position have smoothly reacted to give the desired allyl−alkenyl coupling products in good yields. As anticipated, however, this allyl−alkenyl coupling has proven to be more readily prone to regio- and/or stereoscrambling than the previously developed alkenyl−allyl coupling.[8] (2) The Pd-catalyzed allyl−alkenyl coupling proved to be exactly what was needed for converting the alkyne bromoboration product **3** into one of the key intermediates **4** for the synthesis of yellow scale pheromone (**1**), which proceeded in 77% yield without being accompanied by any isomerization or unwanted debromoboration of **3** to detectable extents. (3) The other key intermediate **2** was prepared in 52% yield as a 99% pure *R* isomer via the ZACA reaction of *t*-$BuPh_2Si$-protected homoallyl alcohol followed by enantiomeric purification by Amano PS lipase-catalyzed acetylation of the unwanted *S* isomer. (4) Iodination of **2** in 97% yield was followed by its in situ lithiation−zincation and Pd-catalyzed cross-coupling of the isoalkylzinc reagent thus generated with the alkenyl iodide **4** cleanly produced isomerically pure (≥98%) **5** in 74% yield from the two iodide precursors. Acetylation of **5** produced the sex pheromone of yellow scale (**1**) of ≥98% isomeric purity even before purification in 34% yield from *t*-$BuPh_2Si$-

(10) (a) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406–5409. (b) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404–5406.

(11) For conceptually related applications of tandem Negishi coupling processes to the synthesis of allenenynes and enediynes, see: (a) Wang, K. K.; Wang, Z. *Tetrahedron Lett.* **1994**, *35*, 1829–1832. (b) Wang, K. K.; Wang, Z.; Tarli, A.; Gannett, P. *J. Am. Chem. Soc.* **1996**, *118*, 10783–10791. (c) Tarli, A.; Wang, K. K. *J. Org. Chem.* **1997**, *62*, 8841–8847.

protected homoallyl alcohol in six steps or in 54% yield from 3-methyl-l-butyne in four steps.

The results presented herein provide yet another example demonstrating the synthetic utility of the ZACA−Pd-catalyzed cross-coupling synergy,[12] which, in this case, is further promoted by alkyne haloboration.

(12) (a) Negishi, E.; Tan, Z.; Liang, B.; Novak, T. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5782–5787. (b) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2911–2914. (c) Magnin-Lachaux, M.; Tan, Z.; Liang, B.; Negishi, E. *Org. Lett.* **2004**, *6*, 1425–1427. (d) Novak, T.; Tan, Z.; Liang, B.; Negishi, E. *J. Am. Chem. Soc.* **2005**, *127*, 2838–2839. (e) Liang, B.; Novak, T.; Tan, Z.; Negishi, E. *J. Am. Chem. Soc.* **2006**, *128*, 2770–2771. (f) Zhu, G.; Negishi, E. *Org. Lett.* **2007**, *9*, 2771–2774. (g) Zhu, G.; Liang, B; Negishi, E. *Org. Lett.* **2008**, *10*, 1099–1101.

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Supporting Information Available: Experimental details and representative ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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