DOI: 10.1002/ejoc.200600721

Construction of Highly Substituted Stereodefined Dienes by Cross-Coupling of α-Allenic Acetates

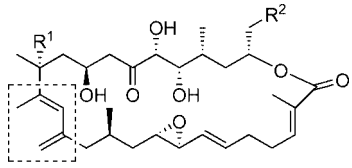
John S. Schneekloth Jr.,[a] Mathieu Pucheault,[b] and Craig M. Crews*[a–c]

Keywords: Cross-coupling / Allenes / Alkenes

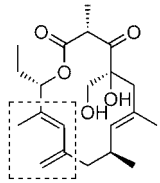
The assembly of highly substituted dienes remains a challenge for organic chemistry. This work represents a strategy for the construction of highly substituted 1,3-dienes by means of a Tsuji–Trost cross coupling between α-allenic acetates and organozinc reagents. The reaction is high yielding, and installs a trisubstituted olefin with *E*/*Z* selectivities up to 95:5 favoring the (*E*) product. A cheap, commercially available palladium precatalyst and a ligand are used to control the *E*/*Z* selectivity. Furthermore, an interesting reversal in selectivity is noted in which appropriate choice of ligand may be used to control the outcome of the reaction and favor the (*Z*) product. Thirteen examples are described, highlighting the substrate scope of the reaction. It is hoped that the straightforward reaction conditions and high selectivity will make this reaction of broad use in natural product chemistry.

Introduction

The synthesis of highly substituted 1,3-dienes remains an important challenge in synthetic chemistry. In addition to being useful substrates for Diels–Alder cycloadditions, highly substituted dienes are prevalent in a number of biologically active polyketide-based natural products such as amphidinolide B[1] and galbonolide B[2] (Figure 1). While a variety of methods are available for constructing dienes through the formation of sp^2–sp^2 carbon–carbon bonds,[3–5] these methods are not always useful in complex systems.[6] Surprisingly, there are few robust methods available to construct dienes with the substitution pattern shown in Figure 1.[7] As part of a program directed towards the total synthesis of amphidinolide B,[8,9] we reported that an α-allenic acetate could be used in a palladium-catalyzed cross-coupling reaction with an organometallic reagent to form a highly substituted stereodefined 1,3-diene.[8] Due to the success of this early observation, we sought to develop this reaction into a general method for the construction of a variety of highly substituted stereodefined dienes. Herein we report a general method for the efficient, stereoselective coupling of α-allenic acetates with a variety of organozinc compounds to form highly substituted, stereodefined (*E*)-dienes (Scheme 1). Furthermore, we report a dramatic, ligand-dependent reversal of *E*/*Z* selectivity in the reaction. The reaction is high yielding and tolerant to a wide variety of organozinc nucleophiles as well as to the nature of the allenic acetate. Previous work in this area has been sparse, although there have been other isolated reports of coupling organoboron or organozinc reagents with allenic acetates.[10–14] Specifically, this work represents the first attempt to install a stereodefined diene containing a differentially functionalized trisubstituted olefin by cross coupling of an allenic acetate.[15,16]



Amphidinolide B: R^1 = OH, R^2 = H
Amphidinolide H: R^1 = H, R^2 = OH

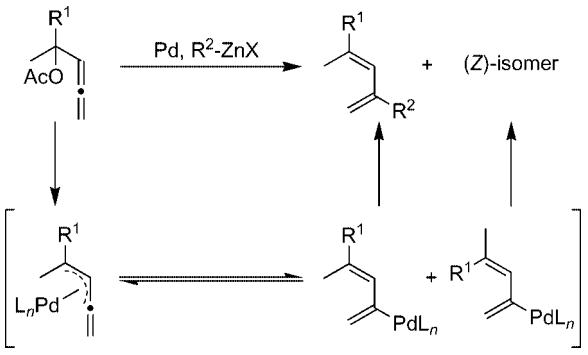


Galbonolide B

Figure 1. Natural products containing the *E*-substituted *s-cis*-diene motif.

[a] Departments of Chemistry, Yale University,
New Haven, CT 06520, USA
E-mail: craig.crews@yale.edu
[b] Departments of Molecular, Cellular, and Developmental Biology,
Yale University, New Haven, CT 06520, USA
[c] Departments of Pharmacology, Yale University,
New Haven, CT 06520, USA

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



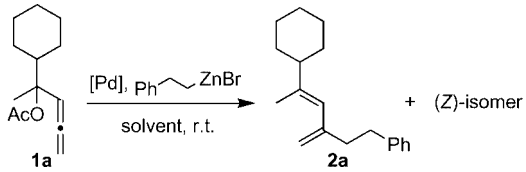
Scheme 1. Cross coupling of α-allenic acetates with organozinc compounds and proposed reaction mechanism.

Results and Discussion

We anticipated that allenic acetates would behave like allylic acetates in that a π–σ–π-type isomerization could occur, and appropriate modulation of reaction conditions could give rise to either the *E*- or *Z*-substituted product (Scheme 1). Initially, we sought mild reaction conditions, as it was postulated that high reaction temperatures would likely lead to lower *E*/*Z* selectivity. Palladium-catalyzed Tsuji–Trost[17] and Negishi[18] type cross-coupling reactions typically proceed under mild conditions, and it was expected that by fine tuning the reaction conditions the steric difference between the methyl group and R^1 could be exploited to generate a large selectivity favoring the (*E*)-substituted product over the (*Z*)-substituted isomer. Toward this end, we synthesized the substrate **1a**, bearing methyl and cyclohexyl substituents on the α-allenic carbon, which was hoped to exhibit a moderate selectivity.

The experiments described in Table 1 detail this optimization. As the S_N2' reaction of allenic acetates has been reported previously,[19] it was important to determine that the reaction was in fact catalyzed by palladium, and not proceeding through a direct substitution mechanism. Table 1, Entry 2, verifies that the reaction only occurs in the presence of catalyst. While our initial experiment using $[Pd(PPh_3)_4]$ achieved high conversion, *E*/*Z* selectivity was poor. In order to examine the effect of varying the ligand, we screened a variety of monodentate and bidentate phosphane ligands.[20] Trialkyl and triarylphosphanes generally afforded high conversion, but lower selectivity (Entries 8, 9). Uniformly, bidentate ligands induced a higher *E*/*Z* selectivity than even the bulkiest monodentate ligands. Wide bite angle ligands such as dppp and dppf afforded the highest *E*/*Z* ratio. Screening a variety of palladium precursors revealed that $[Pd_2dba_3]$ was the most effective in terms of selectivity. Examining a variety of solvents indicated that generation of the catalyst in toluene, followed by addition of the organozinc reagent in THF afforded the best overall selectivity. Finally, conducting the reaction at 0 °C for 12 h afforded diene **2a** in 85% isolated yield with an optimized *E*/*Z* selectivity of 92/8.

Table 1. Reaction optimization.



Entry	[Pd][a]	Ligand	Solvent	Conv. (%)[b]	*E*/*Z* Ratio
1	$[Pd(PPh_3)_4]$	–	THF	100	55:45
2	–	–	THF	0	n/a
3	$[Pd(OAc)_2]$	dppp	THF	51	86:14
4	$[Pd(OAc)_2]$	dppf	THF	100	84:16
5	$[Pd(allyl)Cl_2]$	dppp	THF	23	79:21
6	$[Pd(MeCN)_2Cl_2]$	dppp	THF	34	86:14
7	$[Pd_2dba_3]$	dppp	THF	100	88:12
8	$[Pd_2dba_3]$	PCy_3	THF	100	77:23
9	$[Pd_2dba_3]$	PBu_3	THF[c]	100	59:41
10	$[Pd_2dba_3]$	BINAP	THF	100	91:9
11	$[Pd_2dba_3]$	dppf	THF	88	84:16
12	$[Pd_2dba_3]$	dppf	MeCN	89	89:11
13	$[Pd_2dba_3]$	dppf	CH_2Cl_2	83	90:10
14	$[Pd_2dba_3]$	dppf	toluene	100	90:10
15	$[Pd_2dba_3]$	dppf	toluene[c]	100	92:8

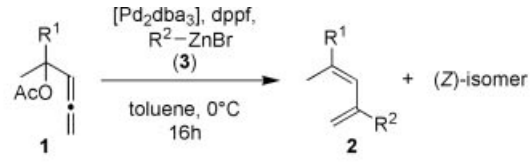
[a] 5 mol-% of palladium catalyst was used. [b] Conversion measured by ^1H NMR after 12 h of reaction time. [c] Reaction conducted at 0 °C. Cooling the reaction to –20 °C was found to slow the reaction considerably, with little increase in selectivity.

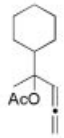
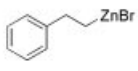
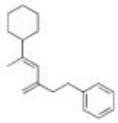
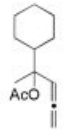
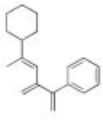
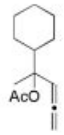
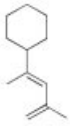
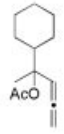
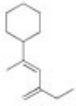
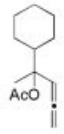
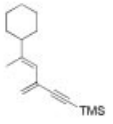
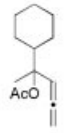
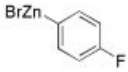
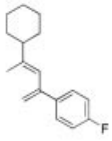
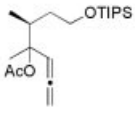
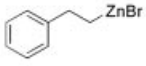
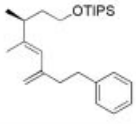
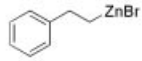
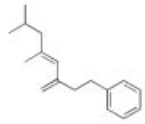
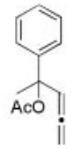
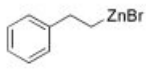
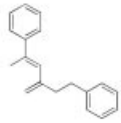
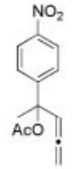
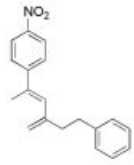
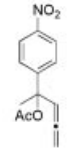
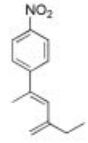
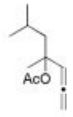
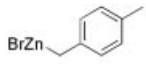
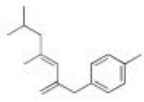
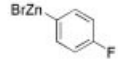
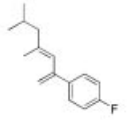
Having optimized the reaction to produce **2a**, we next looked to vary the nature of the organozinc reagent (Table 2). We observed good selectivity irrespective of the nature of the organozinc compound (Table 2).[21] Good chemical yield and *E*/*Z* selectivity were observed when **1** was coupled with alkyl-, vinyl-, and arylzinc halides, as well as with dialkylzinc compounds. An alkynylzinc organometallic reacted with good selectivity, but only moderate yield. In all cases, the *E*/*Z* selectivity was high, with a typical yield of greater than 80%. A benzylzinc partner was also found to be effective (entry 12).

We next examined the effect of the R^1 substituent (Table 2). Coupling of phenethylzinc bromide with a variety of substituted α-allenic acetates revealed that the reaction is tolerant to a variety of functionalities. Use of a second branched R^1 substituent afforded a product with good yield and high selectivity (Entry 7). Electron-poor aryl and phenyl substituents are also easily obtained with excellent yield and selectivity (entries 9–11). Even when R^1 is isobutyl (Entries 8, 12, and 13), the subtle steric difference between methyl and isobutyl substituents can be exploited to obtain the (*E*) product with reasonable selectivity.

Although most ligands tested favored the (*E*)-substituted diene product, this was not the case for every example. As described in Scheme 2, the coupling reaction underwent a dramatic reversal of selectivity when the bulky biaryl phosphane ligand **4** developed by Buchwald and co-workers was used.[22] While the overall yield of the reaction was still high, the major product isolated from the reaction was the (*Z*)-substituted diene in a ratio of 74:26. This effect is not

Table 2. Substrate scope of the cross-coupling reaction.

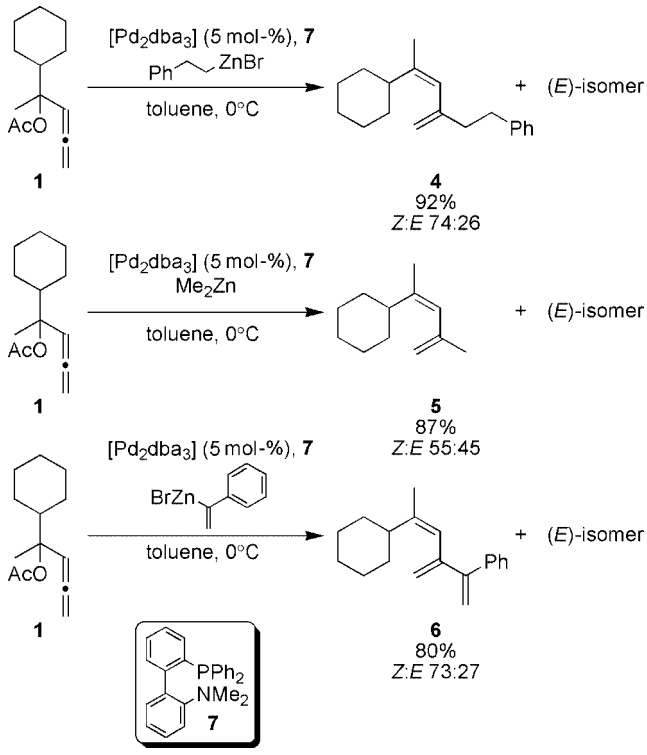


Entry	1	3[a]	Product 2	Yield	*E*/*Z* ratio
1				85%	92:8
2				81%	90:10
3		Me_2Zn[b]		95%	93:7
4		Et_2Zn[b]		94%	94:6
5				47%	92:8
6				92%	88:12
7				87%	86:14
8				91%	84:16
9				87%	95:5
10				88%	95:5
11		Et_2Zn[b]		68%	87:13
12				78%	85:15
13				75%	81:19

[a] Organozinc bromides were used as an 0.5 M solution in THF. [b] Me_2Zn and Et_2Zn were used as a 1.0 M solution in THF. [c] The alkynylzinc triflate was prepared from the corresponding alkyne and zinc(II) triflate with Et_3N as an 0.1 M solution in THF.

limited to **1**; several other substrates tested under identical conditions also slightly favored the (*Z*) isomer (Scheme 2). Although the mechanistic implications of this result are unclear, it raises the possibility that the intermediate is formed by a different mechanism, which can be controlled to favor the thermodynamically less stable (*Z*) product.

In conclusion, we have reported a highly selective cross-coupling reaction between α-allenic acetates and a variety of organozinc nucleophiles to prepare several highly substituted, stereodefined dienes. The reaction is highly tolerant to the nature of the organozinc species, and high selectivity is observed with several differentially substituted allenic acetates. The reaction proceeds with a cheap, commercially available catalyst precursor and ligand. Depending on the ligand used, it is possible to control the reaction to favor highly the (*E*)-substituted product, or slightly favor the (*Z*)



Scheme 2. Reversal of *E*/*Z* selectivity using a biarylmonophosphane.

product. It is hoped that this methodology will find use in the preparation of important biologically active molecules such as the amphidinolides or galbonolides, and studies directed towards such a goal will be reported in due course.

Experimental Section

General Procedure for the Coupling of α-Allenic Acetates with Organozinc Reagents. Synthesis of 2a: To a stirred solution of $[Pd_2dba_3]$ (5.7 mg, 6.2 μM) and 1,1′-bis(diphenylphosphanyl)ferrocene (12.8 mg, 23 μM) in anhydrous toluene (1 mL) under nitrogen was added 2-phenethylzinc bromide (solution in THF 0.5 M, 0.3 mmol, 600 μL). The resulting solution was stirred 10 min at room temperature then cooled to 0 °C. After 5 min at 0 °C, 2-cyclohexylpenta-3,4-dien-2-yl acetate (**1a**, 0.25 mmol, 54 mg, 53 μL) was added and the mixture was maintained at 0 °C for 12 h (monitored by TLC, eluent hexane/AcOEt, 95:5). The mixture was then diluted with hexane (10 mL) and washed with saturated NH_4Cl (2 × 10 mL), saturated sodium hydrogen carbonate (10 mL) and water (3 × 10 mL). The organic fraction was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes to afford 54 mg of **2a** (5-cyclohexyl-3-methylenehex-4-enyl)benzene as a clear, colorless oil (85%, *E*/*Z* = 92:8).

Supporting Information (see also the footnote on the first page of this article): General procedures for the preparation of α-allenic acetates, full spectroscopic data for **1a**–**e** and diene products described in Table 2.

Acknowledgments

The authors would like to thank Professors John Wood and Glenn Micalizio for helpful discussion during the preparation of the manuscript. J. S. S. thanks the American Chemical Society, Division of Medicinal Chemistry and Aventis Pharmaceuticals for a predoctoral fellowship. M. P. thanks the Human Frontier Science Program Organization for a cross-disciplinary postdoctoral fellowship. We thank the NIH (GM062120) for funding.

[1] M. Ishibashi, Y. Ohizumi, M. Hamashima, H. Nakamura, Y. Hirata, T. Sasaki, J. Kobayashi, *J. Chem. Soc., Chem. Commun.* **1987**, 1127–1129.
[2] H. Achenbach, A. Muhlenfeld, H. Zahner, *Tetrahedron Lett.* **1985**, *26*, 6167–6170.
[3] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.
[4] J. Tsuji, Palladium Reagents and Catalysts: Innovations, in: Organic *Synthesis* John Wiley and Sons, Chinchester, **1995**, p. 560.
[5] Metal-catalyzed Cross-coupling Reactions (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, p. 517.
[6] M. B. Cid, G. Pattenden, *Tetrahedron Lett.* **2000**, *41*, 7373–7378.
[7] J. J. Eshelby, P. J. Parsons, N. C. Sillars, P. J. Crowley, *J. Chem. Soc., Chem. Commun.* **1995**, 1497–1498.
[8] A. K. Mandal, J. S. Schneekloth, C. M. Crews, *Org. Lett.* **2005**, *7*, 3645–3648.
[9] A. K. Mandal, J. S. Schneekloth, K. Kuramochi, C. M. Crews, *Org. Lett.* **2006**, *8*, 427–430.
[10] T. Moriya, T. Furuuchi, N. Miyaura, A. Suzuki, *Tetrahedron* **1994**, *50*, 7961–7968.
[11] H. Kleijn, H. Wertmijze, J. Meijer, P. Vermeer, *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 378–380.
[12] J. Nokam, A. Maihara, J. Tsuji, *Tetrahedron Lett.* **1990**, *31*, 5629–5630.
[13] B. M. Trost, D. R. Fandrick, D. C. Dinh, *J. Am. Chem. Soc.* **2005**, *127*, 14186–14187.
[14] D. Djahanbini, B. Cazes, J. Gore, *Tetrahedron* **1987**, *43*, 3441–3452.
[15] S. M. Ma, *Chem. Rev.* **2005**, *105*, 2829–2871 and references cited therein.
[16] R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067–3125, and references therein.
[17] a) J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.* **1965**, *6*, 4387–4388; b) B. M. Trost, T. J. Fullerton, *J. Am. Chem. Soc.* **1973**, *95*, 292–294. For a review: c) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422.
[18] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821–1823. For a review: b) E.-I. Negishi, in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, New York, **1998**, chapter 1; c) E. Erdik, *Tetrahedron* **1992**, *48*, 9577–9648.
[19] A. Horvath, J. E. Bäckvall, *J. Org. Chem.* **2001**, *66*, 8120–8126.
[20] Ligands were purchased from Strem Chemicals or Aldrich Chemicals.
[21] Organozinc reagents were purchased from Aldrich Chemicals.
[22] M. C. Harris, O. Geis, S. L. Buchwald, *J. Org. Chem.* **1999**, *64*, 6019–6022.

Received: August 16, 2006
Published Online: November 21, 2006

