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Tetrahedron Letters 46 (2005) 225–228
Tetrahedron Letters

Pd-catalyzed cross-coupling reaction of (*Z*)- and (*E*)-bromoenyne: unusual stereochemical outcome

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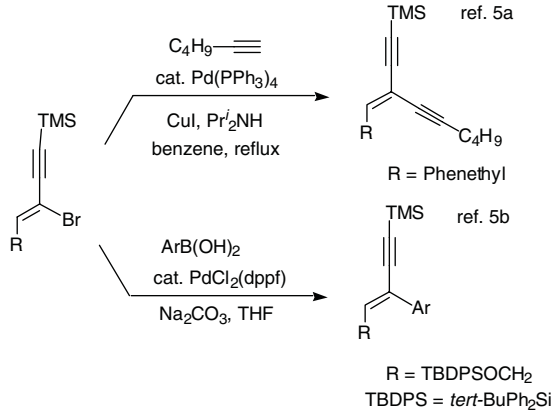
Received 27 October 2004; revised 12 November 2004; accepted 12 November 2004
Available online 26 November 2004

Abstract—Pd-catalyzed cross-coupling reaction of (*E*)-bromoenyne **1***Z* with 1-alkyne and tributylvinyl–stannane occurs with retention of the configuration in benzene but with an inversion of the configuration in DMF or CH_2Cl_2. On the other hand, that of (*Z*)-bromoenyne **1***E* occurs with retention of the configuration in these solvents.

Pd-catalyzed cross-coupling reactions have been used widely in modern organic synthesis.[1] The reactions involve the oxidative addition of Pd to a carbon–halogen bond, *trans*-metallation of an organometallic reagent, and the reductive elimination of Pd to provide cross-coupling products. Cross-coupling of alkenyl halide with alkynyl, alkenyl, and alkyl metals undergoes regio- and stereospecifically to give sp^2–sp,[2a] sp^2–sp^2,[2b] and sp^2–sp^3[2c] carbon–carbon bonds, respectively. Since Pd-catalyzed cross-couplings generally retain geometries of starting alkenyl halides and organometallic reagents[3] (Scheme 1), they have been used for reliable stereospecific carbon–carbon bond forming reactions in a large number of stereospecific syntheses.[4] In fact, we reported the stereospecific Sonogashira and Suzuki coupling reactions of bromoenynes with the retention of the configuration[5] (Scheme 2). However, we have experienced an unexpected solvent-depending stereochemical inversion in the Sonogashira coupling of bromoenyne (**1***Z*) as shown in Scheme 3. In this letter, we disclose the unusual stereochemistry of Pd-catalyzed cross-coupling reactions in the case of bromoenyne.

Scheme 1. Pd-catalyzed cross-coupling of alkenyl halide with organometallic reagent.



Scheme 2.

The coupling reactions of bromoenynes, **1***Z* and **1***E*, with some terminal alkynes were examined. The results are listed in Table 1. Sonogashira coupling of (*Z*)-3-bromo-5-(*tert*-butyldiphenylsilyl)oxy-1-trimethylsilyl-3-penten-1-yne (**1***Z*) with 1-hexyne in benzene in the presence of $PdCl_2$(dppf), CuI, and diisopropylamine gave **2***E* with a 86:14 ratio in 87% yield (entry 1), which was a normal coupling product with retention of the configuration.[5a] However, when the reaction was conducted in DMF, a (*Z*)-isomer **2***Z* was obtained exclusively in 79% yield (entry 6). These stereochemistries were determined by NOE experiments after the partially saturated compounds were derived from the

Keywords: Bromoenyne; Sonogashira coupling; Stille coupling, Enediyne; Stereocontrol.
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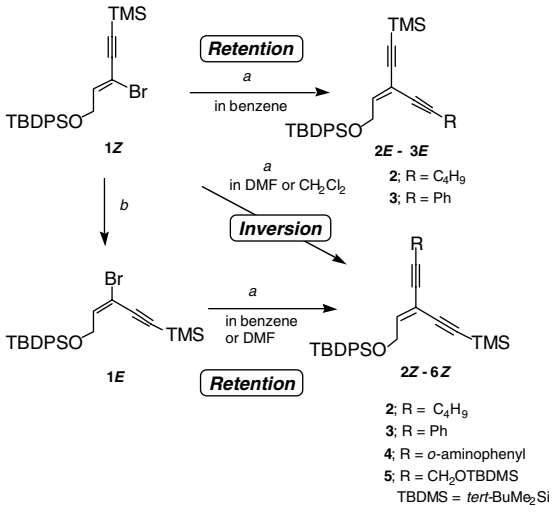
doi:10.1016/j.tetlet.2004.11.061



Scheme 3. Reagents and conditions: (a) ≡–R (5 equiv), 5 mol% $PdCl_2$(dppf), CuI (4 mol%), *i*-Pr_2NH (5 equiv), rt–50°C, 1–12 h, (b) cat iodine, benzene, rt, 2 h then separation by HPLC.

chemoselective reduction of a triple bond to alkane for silylethynyl group over hexynyl group.[6] On the other hand, the same reaction of the geometrical isomer **1***E*, which resulted from the isomerization of **1***Z* and successive separation from the resulting (*E*)- and (*Z*)-mixtures,[7] with 1-hexyne, gave **2***Z* exclusively either in benzene or DMF (entries 11 and 12). The reaction of **1***Z* with 1-hexyne in other solvents such as toluene, THF, and DME gave **2***E* as a major isomer (entries 2–4). While, in CH_2Cl_2 the reaction took place with an inversion of the stereochemistry, giving **2***Z* preferentially (entry 5). A similar trend was observed in the coupling of **1***Z* with phenylethyne, thus the reaction proceeded with retention in benzene giving **3***E* while with inversion in CH_2Cl_2 giving **3***Z* (entries 7 and 8). The coupling of **1***Z* with other alkynes in CH_2Cl_2 gave (*Z*)-enediynes exclusively (entries 9 and 10).

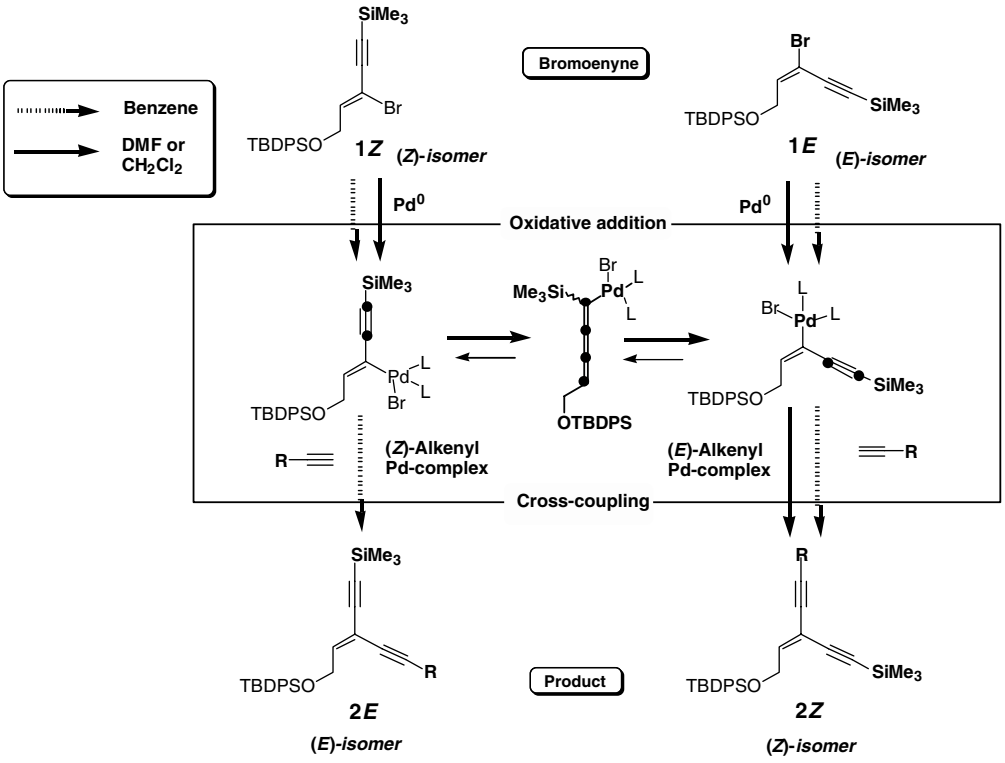
It is quite unusual that a cross-coupling reaction proceeds not stereospecifically but stereoselectively. Particularly, the opposite geometric isomer can be obtained in the choice of solvent. This solvent-dependent stereochemical outcome can be explained by a rearrangement of alkenyl–Pd intermediate shown in Scheme 4. Initially, a sigma-Pd–Br complex is generated from **1***Z* with Pd^0 species. Since this (*Z*)-alkenyl Pd-complex having a large bidentate ligand may repulse the silyloxymethyl group located at the *cis*-position, an isomerization to (*E*)-alkenyl Pd-complex takes place via a cummulenyl Pd-complex by the 1,3-metal migrations.[8] This *trans*-relationship of alkenyl–Pd and $TBDPSOCH_2$ groups tolerates from steric repulsion that exists in the *cis*-isomer. This isomerization and successive cross-coupling yield **2***Z* with the inversion of the configuration. In DMF or CH_2Cl_2, the (*Z*)-alkenyl Pd-complex is easily transformed to the (*E*)-alkenyl Pd-complex via the cummulenyl intermediate. On the other hand, the (*E*)-alkenyl Pd-complex derived from **1***E* undergoes *trans*-metallation without isomerization to give **2***Z*. In benzene the isomerization is suppressed, but does take place in DMF or CH_2Cl_2. Probably, the sigma-Pd-complex could be stabilized favorably in benzene but would become destabilized in DMF or CH_2Cl_2.

We examined other bromoenyne substrates. The reaction of (*Z*)-3-bromo-5-(*tert*-butyldiphenylsilyl)oxy-1-phenyl-3-penten-1-yne (**7***Z*) with TMS–ethyne afforded **3***Z* in 73% yield preferentially in benzene with a 9:1 ratio. On the other hand, the isomer **3***E* was yielded in CH_2Cl_2 in the opposite ratio in 71% yield. Although the reaction of **7***Z* with TMS–ethyne in benzene gave **3***Z* with the retention of the configuration, that of **8***Z* in which the amino group was substituted at the *ortho*-position of **7***Z*, gave an inversion product **4***E* preferentially in an 88:12 ratio in 66% yield, in which the minor retention product **4***Z* was identified to be the major product obtained from **1***Z* with *o*-aminophenylethyne (entry 9 in Table 1). These results are quite interesting, because the presence or absence of the *ortho*-amino group located on the phenyl ring has controlled the stereochemistry of the product.[9] It is noteworthy that the inversion reaction takes place even in benzene in

Table 1. Sonogashira coupling of (*E*)- and (*Z*)-bromoenynes (1*E* and 1*Z*) with terminal alkynes

Entry	Bromoenyne	Alkyne	Solvent	Product	Ratio[a] *E*:*Z*	Major isomer	Yield (%)
1	**1***Z*	1-Hexyne	Benzene[b]	**2***E*:**2***Z*	86:14	Ret.	87
2	**1***Z*	1-Hexyne	toluene[b]	**2***E*:**2***Z*	89:11	Ret.	90
3	**1***Z*	1-Hexyne	THF[b]	**2***E*:**2***Z*	84:16	Ret.	97
4	**1***Z*	1-Hexyne	DME[b]	**2***E*:**2***Z*	75:25	Ret.	58
5	**1***Z*	1-Hexyne	CH_2Cl_2[c]	**2***E*:**2***Z*	16:84	Inv.	64
6	**1***Z*	1-Hexyne	DMF[b]	**2***E*:**2***Z*	3:97	Inv.	79
7	**1***Z*	Ph—≡	Benzene[b]	**3***E*:**3***Z*	78:22	Ret.	76
8	**1***Z*	Ph—≡	CH_2Cl_2[c]	**3***E*:**3***Z*	0:100	Inv.	82
9	**1***Z*	*o*-aminophenyl—≡	CH_2Cl_2[c]	**4***E*:**4***Z*	0:100	Inv.	78
10	**1***Z*	$TBDMSOH_2C$—≡	CH_2Cl_2[c]	**5***E*:**5***Z*	0:100	Inv.	68
11	**1***E*	1-Hexyne	Benzene[b]	**2***E*:**2***Z*	0:100	Ret.	82
12	**1***E*	1-Hexyne	CH_2Cl_2[c]	**2***E*:**2***Z*	0:100	Ret.	58

[a] The ratio was determined by proton NMR.
[b] 50 °C.
[c] Refluxing temperature.

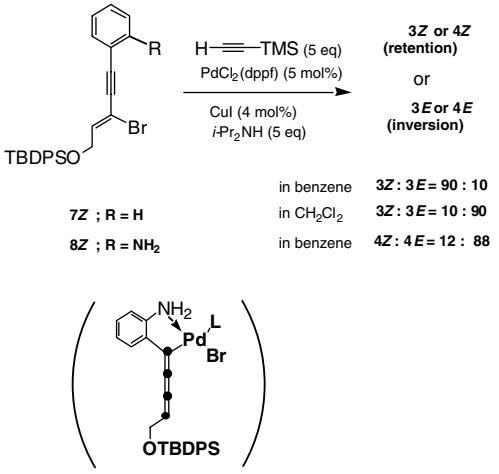


Scheme 4.

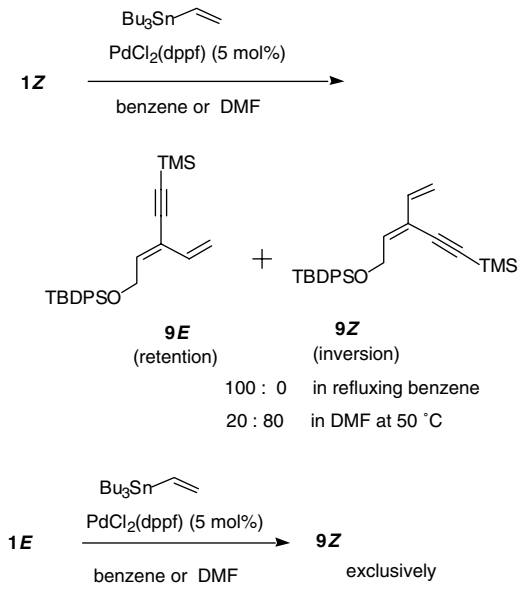
the case of **8***Z*. This fact indicates that the amino group can stabilize the intermediary cummulenyl Pd-complex by the coordination effect, as shown in Scheme 5. Although a product derived from the cummulenyl Pd-complex could not be isolated at all, this fact would strongly support the equilibrium between the alkenyl and cummulenyl Pd-complex intermediates.[10]

If this is correct, we may be able to observe this particular inversion and retention stereochemistry being controlled by solvents in other Pd-catalyzed cross-coupling reactions. We examined Stille coupling for **1***Z* and **1***E* shown in Scheme 6. Indeed, the reaction of **1***Z* with tributylvinylstannane in the presence of $PdCl_2$(dppf) proceeded in benzene to give the retention product **9***E* exclusively in 75% yield, and in DMF to give the inversion product **9***Z* preferentially in 80% with an 87:13 ratio. On the other hand, the same reaction of **1***E* with tributylvinylstannane afforded **9***Z* in 75–85% yield either in benzene or DMF. These results are consistent with those of Sonogashira coupling of bromoenyne.

In conclusion, we have found that the choice of solvent has an impact on the stereocontrol of the Pd-catalyzed cross-coupling reaction of bromoenyne. This occurred



Scheme 5.



Scheme 6.

in the specific case of Pd-catalyzed cross coupling of bromoenyne, though this method could be useful for the preparation of carbon-conjugated trisubstituted enediyne as well as dienynes.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.061.

References and notes

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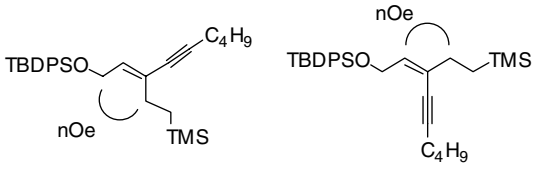
6. Treatment of **2***E* and **2***Z* with an excess of diimide generated from dipotassium diazodicarboxylate with acetic acid in THF, reduced trimethylsilylethynyl function chemoselectively to trimethylsilylethyl function, respectively. Their geometries were determined by the NOE experiments, shown below.



This protocol was reported previously, see: Uenishi, J.; Matsui, K.; Ohmiya, H. *J. Organomet. Chem.* **2002**, *653*, 141–149.
7. Isomerization was carried out in $CHCl_3$ at room temperature for 12 h in the presence of iodine (0.1 equiv) and gave a 1:1 mixture of **1***Z* and **1***E*. ^1H NMR in $CDCl_3$ (selected) **1***Z* δ 0.22 (9H, s), 1.05 (9H, s), 4.34 (2H, d, $J = 5.3$ Hz), 6.55 (1H, t, $J = 5.3$ Hz). **1***E* δ 0.10 (9H, s), 1.56 (9H, s), 4.32 (2H, d, $J = 6.6$ Hz), 6.46 (1H, t, $J = 6.6$ Hz).
8. To our best knowledge, this is a quite rare example except one. The isomerization of (*E*)- and (*Z*)-1-alkynyl-1-alkenyl lithium via cummlenyl lithium intermediate was proposed and methylation of bromoenyne was reported without a description of the detail. See: Miller, J. A.; Leong, W.; Zweifel, G. *J. Org. Chem.* **1988**, *53*, 1839–1840.
9. *o*-Benzylidenylimino group instead of ortho amino group also induced a similar stereochemical result.
10. It is quite interesting that $Pd(^tBu_3P)_2$ catalyzed alkylation of 3-bromo-3-en-1-yne with alkylzinc reagent took place with retention of the configuration. Shi, J.; Zeng, X.; Negishi, E. *Org. Lett.* **2003**, *5*, 1825–1828.