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Highly Efficient and Selective Synthesis of Conjugated Triynes and Higher Oligoynes of Biological and Materials Chemical Interest via Palladium-Catalyzed Alkynyl–Alkenyl Coupling[†]

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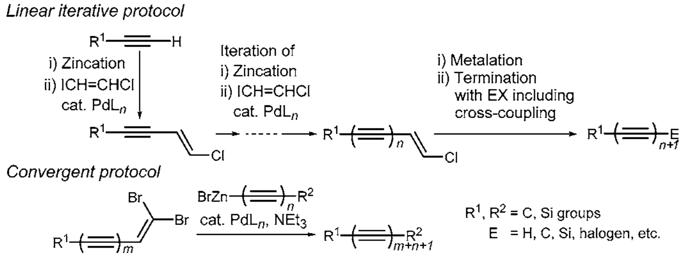
ABSTRACT



Iteration of a Pd-catalyzed reaction of alkynyl- and oligoynylzincs with (*E*)-ICH═CHCl followed by metalation–termination with electrophiles(E) has provided a linear route to conjugated tri- and tetraynes, and Pd-catalyzed monoalkynylation of 1,1-dibromoenynes accompanied by dehydrobromination has provided a convergent route to conjugated tri- , tetra- , and pentaynes. Both display unprecedented high efficiency and selectivity.

A large number of naturally occurring conjugated diynes and oligoynes exhibiting antibacterial, antifungal, antiinflammatory, antiangiogenic, antimicrobial, cytotoxic, larvicidal, and other biological activities are known.[1] Additionally, a growing number of nonnatural oligo- and polyynes of optical, electrical, and other materials as well as structural chemical interest have been prepared and investigated.[2] The parent polyynes of high degrees of polymerization represent the hypothetical sp carbon allotrope "carbyne" of considerable current interest.[2b,3]

Although various Cu-mediated[4] and Pd-catalyzed[5,6] methods for the synthesis of unsymmetrically substituted conjugated diynes via alkynyl−alkynyl coupling are known, the

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[†] **Warning!** Upon concentration and exposure to air, 1-trimethylsilyl-1,3,5,7-nonatetrayne spontaneously ignited in a manner of fireworks. Although the exact nature of the phenomenon remains unclear, it is advisable to exercise appropriate precautions in handling conjugated oligoynes.[3.]

(1) For reviews, see: (a) Bohlmann, F.; Burkhardt, H.; Zdero, C. *Naturally Occurring Acetylenes*; Academic Press: New York, 1973; pp 547. (b) Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1043.

(2) See, for example: (a) Ye, F.; Orita, A.; Yaruva, J.; Hamada, T.; Otera, J. *Chem. Lett.* **2004**, *33*, 528. (b) Gibtner, T.; Hampel, F.; Grisselbrecht, J.-P.; Hirsch, A. *Chem. Eur. J.* **2002**, *8*, 408.

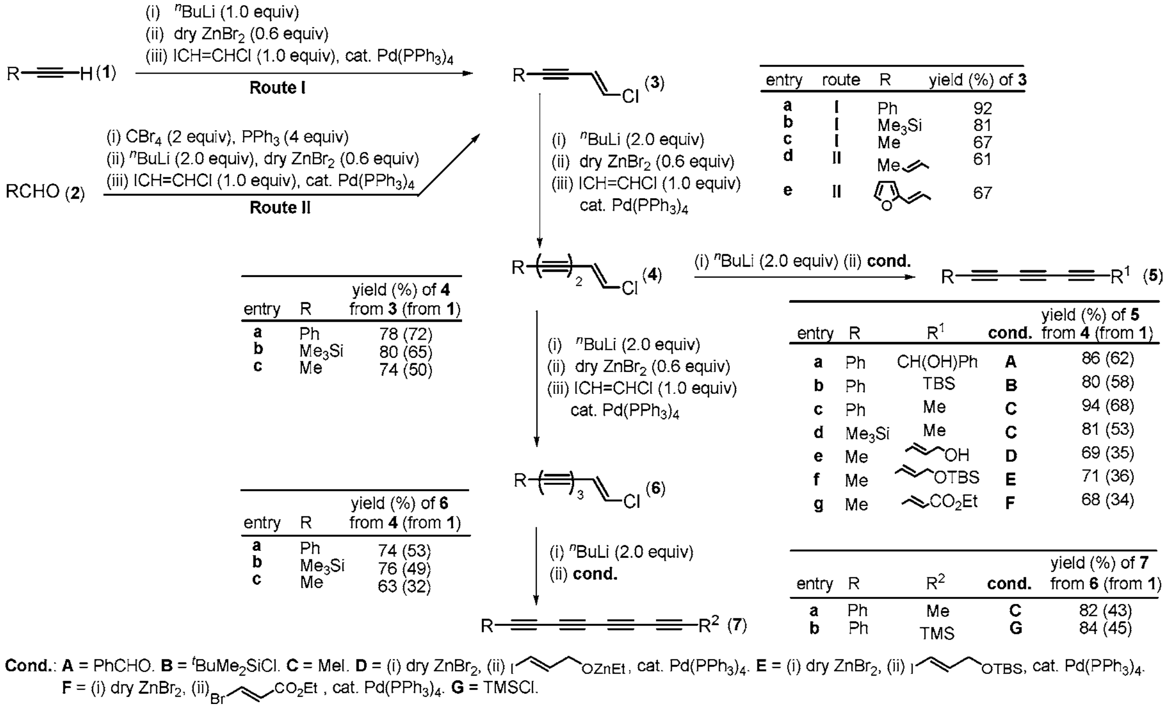
(3) For a recent paper reporting on an explosion of conjugated polyynes, see: Baughman, R. H. *Science* **2006**, *312*, 1009.

(4) (a) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 597−647. (b) Brandsma, L.; Vasilevski, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysis in Organic Synthesis*; Springer-Verlag: Berlin, 1999; pp 49−105.

(5) For a recent review summarizing the reported results of the Pd-catalyzed alkynyl−alkynyl coupling reactions, see: Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

10.1021/ol0623825 CCC: $33.50

Scheme 1



entry	route	R	yield (%) of **3**
a	I	Ph	92
b	I	Me_3Si	81
c	I	Me	67
d	II	Me	61
e	II		67

entry	R	yield (%) of **4** from **3** (from **1**)
a	Ph	78 (72)
b	Me_3Si	80 (65)
c	Me	74 (50)

entry	R	yield (%) of **6** from **4** (from **1**)
a	Ph	74 (53)
b	Me_3Si	76 (49)
c	Me	63 (32)

entry	R	R^1	cond.	yield (%) of **5** from **4** (from **1**)
a	Ph	CH(OH)Ph	**A**	86 (62)
b	Ph	TBS	**B**	80 (58)
c	Ph	Me	**C**	94 (68)
d	Me_3Si	Me	**C**	81 (53)
e	Me	OH	**D**	69 (35)
f	Me	OTBS	**E**	71 (36)
g	Me	CO_2Et	**F**	68 (34)

entry	R	R^2	cond.	yield (%) of **7** from **6** (from **1**)
a	Ph	Me	**C**	82 (43)
b	Ph	TMS	**G**	84 (45)

Cond.: **A** = PhCHO. **B** = $^tBuMe_2SiCl$. **C** = MeI. **D** = (i) dry $ZnBr_2$, (ii) I–OZnEt, cat. $Pd(PPh_3)_4$. **E** = (i) dry $ZnBr_2$, (ii) I–OTBS, cat. $Pd(PPh_3)_4$. **F** = (i) dry $ZnBr_2$, (ii) Br–CO_2Et, cat. $Pd(PPh_3)_4$. **G** = TMSCl.

available data indicate that none appear to be widely and predictably satisfactory, the major side reaction being competitive formation of the two homodimers derivable from the two starting alkynes presumably via alkynyl ligand scrambling. For example, we recently reported a highly cross-selective reaction of $BrZnC{\equiv}CCO_2Me$ with $^nHexC{\equiv}CI$ producing $^nHexC{\equiv}CC{\equiv}CCO_2Me$ in 86% yield[7] but still failed to develop it into a predictably general and satisfactory route to conjugated diynes. An ingenious application of the Fritsch−Buttenberg−Wiechell rearrangement[8] by Tykwinski et al.[1b,9] provides an alternative convergent route to conjugated oligoynes. However, application of these basically convergent protocols to the synthesis of tetra- and higher conjugated oligoynes requires one or two shorter oligoynyl intermediates. In this context, a recent modification of the Cadiot−Chodkiewicz reaction permitting its iterative use by Kim et al.[10] is noteworthy, but each homologation cycle requires two steps, namely, halogenation of alkynylsilanes and alkynyl−alkynyl coupling. It is clearly desirable to develop protocols requiring just one step for each homologation or even less, i.e., homologation by two or more ethynyl units in one step.

We report herein a highly efficient and strictly "pair-selective"[11] linear iterative protocol for the synthesis of conjugated tri- and tetraynes (Schemes 1 and 2). Also reported are some results for the development of a complementary convergent protocol for the synthesis of tri- and higher oligoynes (Schemes 3 and 4) through application of a strictly pair-selective Pd-catalyzed alkynyl−alkenyl coupling.

Since 1984, we have reported a series of pair-selective syntheses of conjugated diynes via Pd-catalyzed alkynyl−alkenyl coupling reactions[12−15] with (*E*)-1-iodo-2-chloroethylene,[12,13] (*E*)-1-iodo-2-bromoethylene,[13] and vinylidene dichloride.[14] However, their applicability to the synthesis of higher oligoynes has not been investigated. In the initial search for a highly favorable ethynyl synthon, conversion of $PhC{\equiv}CH$ to $PhC{\equiv}CC{\equiv}CMe$ was performed with (*E*)-ICH═CHCl,[12,16] (*E*)-ICH═CHBr,[13,17] $Cl_2C{=}CH_2$ ($6.6/mol, Aldrich), and $ClCH{=}CCl_2$ ($1.2/mol, Aldrich) as ethynyl synthons. The yields of $PhC{\equiv}CC{\equiv}CMe$ were 84, 76, 72, and 55%, respectively. Despite the lower product

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(6) For papers reporting the use of Sonogashira alkynyl−aklynyl coupling, see: (a) Wityak, J.; Chan, J. B. *Synth. Commun.* **1991**, *21*, 977. (b) Alzeer, J.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 177. (c) Amatore, C.; Blart, E.; Genêt, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829. (d) Alami, M.; Ferri, F. *Tetrahedron Lett.* **1996**, *37*, 2763.

(7) Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597.

(8) (a) Fritsch, P. *Liebigs Ann. Chem.* **1894**, *279*, 319. (b) Buttenberg, W. P. *Liebigs Ann. Chem.* **1894**, *279*, 327. (c) Wiechell, H. *Liebigs Ann. Chem.* **1894**, *279*, 332.

(9) (a) Eisler, S.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2000**, *122*, 10737. (b) Shi Shun, A. L. K.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 6810. (c) Luu, T.; Shi, W.; Lowary, T. L.; Tykwinski, R. R. *Synthesis* **2005**, 3167. (d) For an application of the Tykwinski protocol to the synthesis of (−)-ichthyothereol, see: Mukai, C.; Miyakoshi, N.; Hanaoka, M. *J. Org. Chem.* **2001**, *66*, 5875.

(10) Kim, S.; Kim, S.; Lee, T.; Ko, H.; Kim, D. *Org. Lett.* **2004**, *6*, 3601.

(11) In place of "pair-selective", a Greek-derived term "couploselective" may be used along with "stereoselective", "regioselective", and so on.

(12) Negishi, E.; Okukado, N.; Lovich, S. F.; Luo, F. T. *J. Org. Chem.* **1984**, *49*, 2629. See also: Kende, A. S.; Smith, C. A. *J. Org. Chem.* **1988**, *53*, 2655.

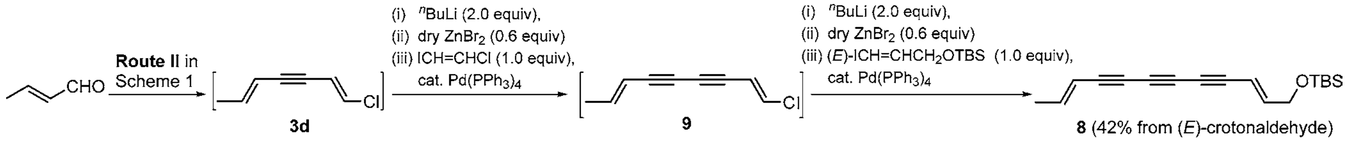
(13) Negishi, E.; Hata, M.; Xu, C. *Org. Lett.* **2000**, *2*, 3687.

(14) Qian, M.; Negishi, E. *Org. Process Res. Dev.* **2003**, *1*, 412.

(15) For a recent review, see: Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71. See also ref 5.

(16) (a) Van de Walle, H.; Henne, A. *Bull. Clin. Sci., Acad. R. Belg.* **1925**, *11*, 360 [*Chem. Abstr.* **1926**, *20*, 1050]. (b) For a detailed procedure, see ref 12.

Scheme 2



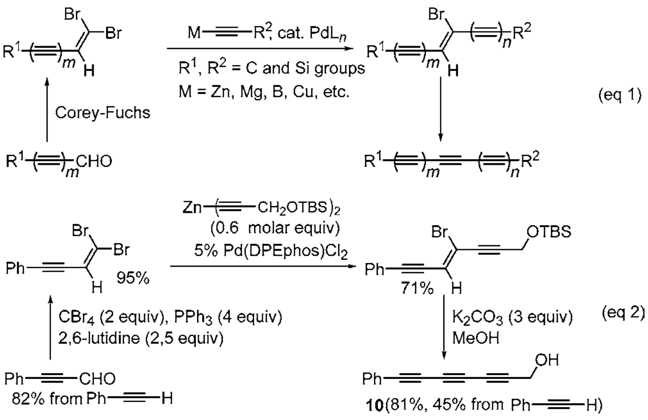
	yield (%)			
procedure	**3d** (from MeCH=CHCHO)	**9** (from **3d**)	**8** (from **9**)	overall (from MeCH=CHCHO)
stepwise synthesis	63	68	71	30
one-pot	–	–	–	42

yields, the significantly lower costs of $Cl_2C{=}CH_2$ and $ClCH{=}CCl_2$ might appear to favor their use in cases where the starting alkynes are relatively inexpensive.

However, their cross-coupling reactions require severalfold excesses of them, which complicates their iterative use for the synthesis of oligoynes. In view of the higher product yield and cleaner reaction profile, (*E*)-ICH═CHCl was chosen in this study. As an ethynyl synthon, (*E*)-ICH═CHBr does not generally offer any notable advantage over (*E*)-ICH═CHCl. Some representative results of the syntheses of tri- and tetraynes from the corresponding monoynes (**1**) or aldehydes (**2**) in three and four steps, respectively, are summarized in Scheme 1. Specifically, several triynes (**5**) were prepared in 34−62% overall yields from **1**, and a couple of tetraynes (**7**) were prepared in 43 and 45% overall yield.

Many of the requisite starting terminal alkynes are commercially available. In cases where appropriately structured aldehydes are economically available, as in the case of (*E*)-crotonaldehyde, 2-furylaldehyde, and (*E*)-3-(2-furyl)-acrolein, the corresponding alkynylzinc reagents can be readily generated via Corey−Fuchs[18] and other carbonyl alkynylation reactions and used in situ for the preparation of **3** in one pot (route II in Scheme 1). An efficient synthesis of a dienetriyne derivative (**8**) from (*E*)-crotonaldehyde, (*E*)-ICH═CHCl, and (*E*)-$ICH{=}CHCH_2OTBS$ in 42% overall yield shown in Scheme 2 is exemplary. In this case, the dienemonoyne (**3d**) and dienediyne (**9**) intermediates were obtained as crudely worked-up materials without purification and used in the subsequent steps. For their full identification, however, they were chromatographically purified and isolated. This additional operation, however, led to an overall yield of 30% for the synthesis of **8**. Omission of purification of intermediates was also applied to the synthesis of 1-phenyl-1,3,5-heptatrieyne (**5c**). Even though the overall yield of 67% from PhC≡CH is only comparable to that shown in entry c (68%), the overall process is simpler and more efficient.[19] In all of the other cases shown in Scheme 1, however, all indicated intermediates were isolated and purified primarily for their full identification.

Scheme 3



During the development of the above-described linear iterative protocol, it occurred to us that 1,1-dibromo-1-alkenes should be used not as mere precursors to 1-alkynes (routes II in Schemes 1 and 2) but for devising a convergent protocol shown in Scheme 3 for the synthesis of triynes and higher oligoynes by combining two shorter monoynyl and/or oligoynyl intermediates, the latter of which are now efficiently and selectively preparable, as discussed above. The critical step involves the Pd-catalyzed trans-selective monoalkynylation of 1,1-dibromo- and 1,1-dichloro-1-alkenes developed recently by us.[20]

For the proof of principle, 7-phenyl-2,4,6-heptatriyn-1-ol (**10**) was prepared in 45% overall yield in four steps from PhC≡CH and $HC{\equiv}CCH_2OTBS$, as shown in eq 2 of Scheme 3.[21,22] Application of the convergent protocol shown in Scheme 3 to the synthesis of conjugated tetraynes, however, was complicated by competitive formation of the expected monobromotriynes and the eventual target tetraynes. Specifically, the reaction of 4-phenyl-1,1-dibromo-1-buten-3-yne with 1.1 equiv of an enediynylzinc derivative **11**, generated in situ by treating (*E*,*E*)-1-chloro-1,5-heptadien-3-yne, in the

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(17) (a) Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, 2, 65. (b) Negishi, E.; Zeng, X. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 2002. (c) Bartlome, A.; Stampfli, U.; Neuschwander, M. *Chimia* **1991**, *45*, 346.

(18) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.

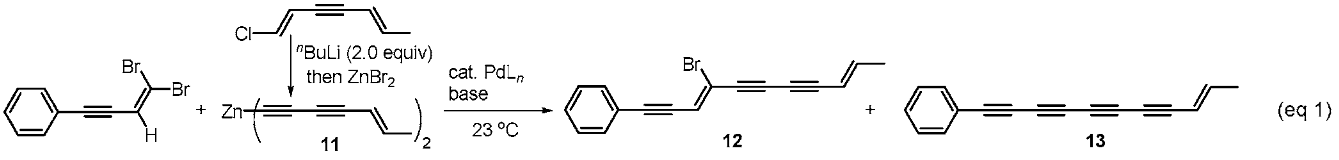
(19) For the synthesis of oligoenynes via the Pd-catalyzed alkynylation through the use of ICH═CHBr involving the formation of two or more C−C bonds without isolation/purification, see: (a) Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65. (b) Ghasemi, H.; Antunes, L. M.; Organ, M. G. *Org. Lett.* **2004**, *6*, 2913.

(20) (a) Shi, J.; Zeng, X.; Negishi, E. *Org. Lett.* **2003**, *5*, 1825. (b) Negishi, E.; Shi, J.; Zeng, X. *Tetrahedron* **2005**, *61*, 9886.

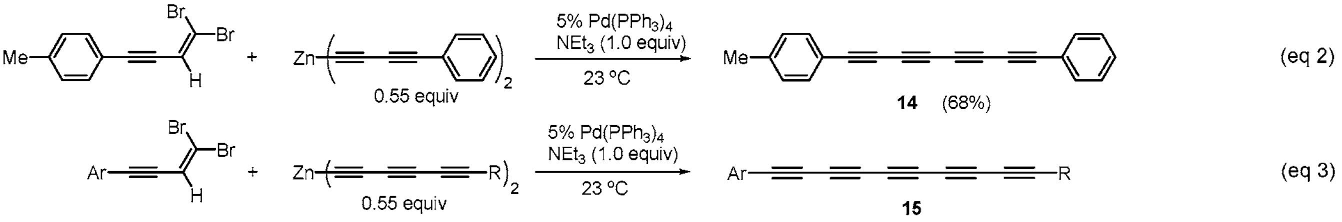
(21) For related syntheses of conjugated diynes, see: (a) Bryant-Friedrich, A.; Neidlein, R. *Synthesis* **1995**, 1506. (b) Shen, W.; Thomas, S. A. *Org. Lett.* **2000**, *2*, 2857.

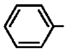
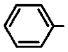
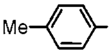
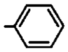
(22) A recent synthesis of **10** from PhC≡CH and $HOCH_2C{\equiv}CCH_2OH$ was achieved in 17% overall yield over seven steps.[9c]

Scheme 4



amount of **11** (molar equiv)	added base	catalyst (%)	yield (%)		
			12	**13**	dibromide
0.55	None	Pd(DPEphos)Cl_2 (5)	<10	32	49
1.0	None	Pd(DPEphos)Cl_2 (5)	<1	66	<1
0.55	NEt_3 (1 equiv)	Pd$(PPh_3)_4$ (5)	<1	66	<1



entry	Ar	R	yield of **15** (%)
a		Me	43
b			48
c			55

presence of 5 mol % of Pd(DPEphos)Cl_2 at 23 °C gave **12** and **13** in <10 and 32% yields, respectively, with 49% of the starting dibromide remaining unreacted. Only traces, if any, of the stereoisomer of **12** and the dialkynylated product were present. Although the precise mechanism of formation of **13** is unclear, **11** must have been partially consumed as a mere base to neutralize HBr. As expected, the use of 2 equiv of **11** produced **13** in 66% yield along with only traces of **12** and the starting dibromide. Although this reaction is clean, it is not synthetically attractive, as it requires 1.0 molar equiv (or a 2-fold excess) of the alkynylzinc reagent. Our recent development of the Pd-catalyzed alkynylation with free terminal alkynes in the presence of NEt_3 and $ZnBr_2$,[23] however, provided a handy solution. Thus, a combination of **11** (0.55 molar equiv) and NEt_3 (1.0 equiv) in place of a 2-fold excess (1.0 molar equiv) of **11** cleanly produced **13** in 66% yield (eq 1 of Scheme 4). This procedure was successfully applied to the synthesis of **14** in 68% yield from 4-(*p*-tolyl)-1,1-dibromo-1-buten-3-yne and bis(4-phenyl-1,3-butadiynyl)zinc (eq 2 of Scheme 4) as well as three conjugated pentaynes **15a**−**c** (eq 3 of Scheme 4).

Although further condition optimization is needed to improve the modest yields of 43−55%, these examples appear to represent the first set of pair-selective syntheses of unsymmetrically substituted conjugated pentaynes.

Acknowledgment. We thank the National Science Foundation (CHE-0309613), the National Institutes of Health (GM 36792), and Purdue University for support of this research.

Supporting Information Available: Experimental details of representative reactions as well as spectral and analytical data of isolated products including ^{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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[23] Anastasia, L.; Negishi, E. *Org. Lett.* **2001**, *3*, 3111.