Pergamon

Tetrahedron Letters, Vol. 37, No. 27, pp. 4679-4682, 1996
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0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00962-8

A Selective Procedure for α-Alkenylation of Enones Involving Pd-Catalyzed Alkenyl-Alkenyl Coupling and Its Application to a Convergent and Efficient Synthesis of Nakienone B

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Abstract: A convergent and efficient synthesis of a marine natural product, nakienone B (**1**), was achieved using a new protocol for α-alkenylation of enones involving Pd-catalyzed coupling of alkenylzincs with alkenyl iodides. This protocol features (i) avoidance of acidic conditions and (ii) flexibility in charge affinity pattern with respect to the two akenyl groups to be coupled.

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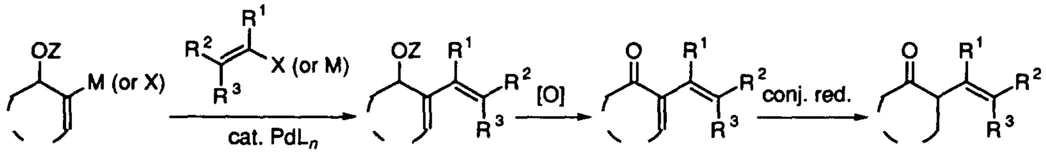
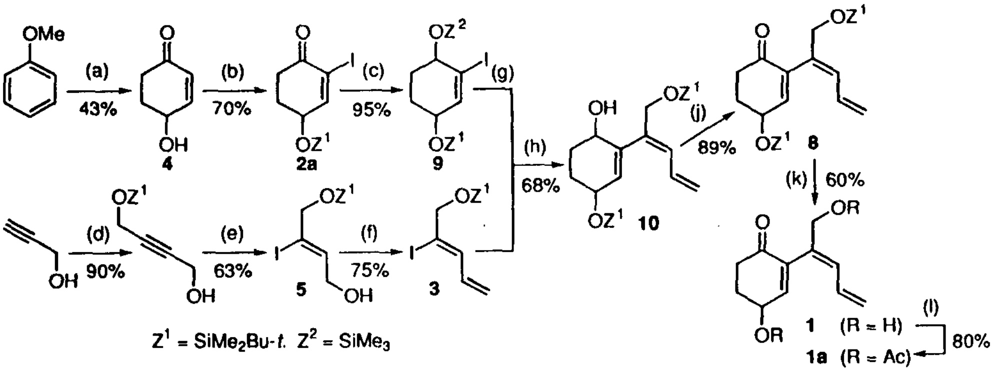
Herein described is a novel and selective protocol for the synthesis of α-alkenylenones, adaptable to the regiospecific synthesis of α-alkenyl ketones, based on the Pd-catalyzed alkenyl-alkenyl cross coupling (Scheme 1). Two main features of the procedure are that no acidic reagents are employed, permitting the synthesis of acid-sensitive compounds and/or the use of acid-sensitive starting materials and intermediates and that it is flexible with respect to the charge affinity pattern for the two alkenyl moieties to be coupled. To demonstrate these advantageous features, a marine natural product, nakienone B (**1**),[1] was synthesized in an efficient and selective manner (Scheme 2).

Regiospecific α-alkenylation of ketones and enones with control of the regio- and stereochemical features of the alkenyl group represents one of the underdeveloped and yet potentially significant synthetic operations. Among relatively rare examples in the literature is the reaction of α-alkoxycarbonyl ketones with alkenyllead triacetates.[2] Some other approaches such as (i) Pd-catalyzed cross coupling of stannyl enol ethers with alkenyl halides,[3] (ii) treatment of ketone enolates with α-silyl aldehydes[4] or enol ether-iron complexes,[5] and (iii) reductive rearrangement of alkenyl halohydrins followed by oxidation[6] either are of limited scope or lack selectivity with respect to regio- and/or stereochemistry. We have previously reported one non-regiospecific[7] (Protocol I) and a few regiospecific[7,8] (Protocols II and III) procedures as summarized in Scheme 3. The scope of Protocol IIIb has been further extended by Johnson, *et al.*[9]

Scheme 1



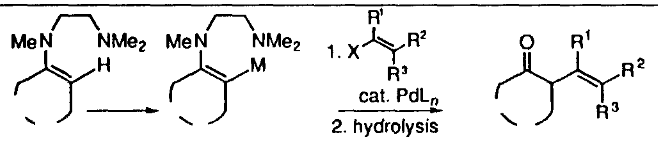
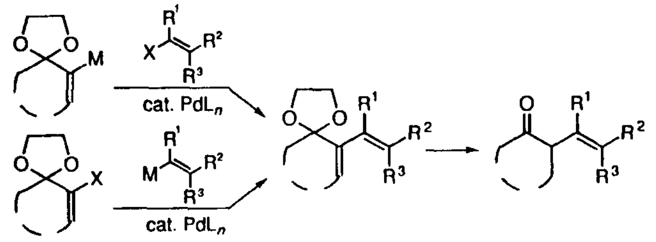
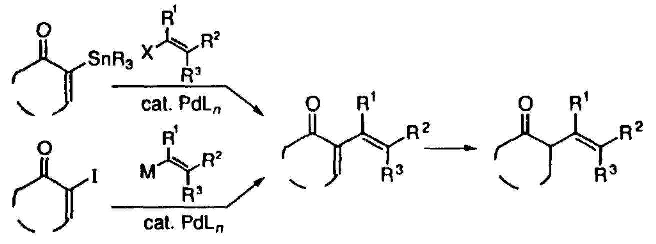
Scheme 2



Z^1 = $SiMe_2Bu$-*t*. Z^2 = $SiMe_3$

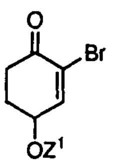
(a) (i) Li (5 equiv), NH_3, *t*-BuOH, -33°C, 2h, (ii) 3/1 MeOH-H_2O, 4% $(COOH)_2$, (iii) m-chloroperoxybenzoic acid, CH_2Cl_2, 12h, (iv) Al_2O_3, Et_2O/CH_2Cl_2, 0.5h. (b) (i) *t*-$BuMe_2SiCl$, DBU, benzene, 1h, (ii) I_2, pyridine, CCl_4, 14h. (c) (i) $NaBH_4$, $CeCl_3.7\,H_2O$, MeOH, 10 min, -20°C, (ii) Me_3SiCl, Et_3N, 14h. (d) (i) i-Pr_2EtN, *t*-$BuMe_2SiCl$, 14h, (ii) n-BuLi, -78°C, 1h, $(CH_2O)_n$, -78 to 25°C. (e) (i) $LiAlH_4$, NaOMe (2.2 equiv), -48°C for 60h and -35°C for 12h, (ii) EtOAc, -20°C, 1h, (iii) I_2 (1.4 equiv), -78 to 25°C. (f) (i) $(COCl)_2$, DMSO (2.2 equiv), -60°C, 20 min, (ii) Et_3N, -60 to 25°C, (iii) $Ph_3P{=}CH_2$, THF, -15°C. (g) (i) n-BuLi, THF-Et_2O-pentane, -110°C, 15 min, (ii) $ZnBr_2$ (0.5 equiv), THF, -110 to 25°C. (h) (i) 5% $Pd(PPh_3)_4$, DMF, 25°C, 6h, (ii) K_2CO_3, MeOH, 25°C, 1h.
(j) (i) $(COCl)_2$, DMSO (4 equiv), -60°C, 2h, (ii) Et_3N (10 equiv), -60 to 25°C. (k) Bu_4NF (4 equiv), THF, 45 min.
(l) Ac_2O, Et_3N, 25°C, 2d.

Scheme 3

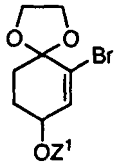
Protocol [a]	Synthetic scheme	Drawback
I[7]		Regioselective routes to the starting enamines have not yet been developed.
IIa[7] IIb[10]		It requires acidic conditions.
IIIa[8] IIIb[8]		Protocol IIIa is of limited scope.

[a] The use of these protocols provided (*E*)-2-(1-octenyl)cyclopentanone (**12**) or (*E*)-2-(1-alkenyl)-2-cyclopenten-1-one (**13**, **a**: 1-octenyl, **b**: 1-hexenyl) in the yields shown in parentheses based on the cycloalkenyl precursors: I (**12**, 78%), IIa (**13a**, 92%, M = Zn), IIIa (**13a**, 80%, X = I), and IIIb (**13b**, 100%, M = Zn).

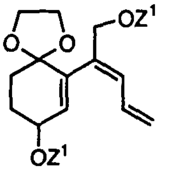
To develop a convergent route to nakienone B (1) via Pd-catalyzed alkenyl-alkenyl coupling, the *t*-BuMe$_2$Si-protected (TBDMS hereafter) 2-iodo-4-hydroxy-2-cyclohexenones (**2a**) and (*Z*)-2-iodo-2,4-pentadien-1-ol (**3**) were prepared as shown in Scheme 2. Anisole was reduced by the Birch reaction. Epoxidation and β-elimination of the crude product gave **4**[11] as a key intermediate. After protection of the OH group, iodination[12] provided **2a**. The corresponding bromo derivative **2b** was prepared by bromination[13] of **4** with Br_2 in CH_2Cl_2 at -40 to 0 °C and then Et_3N at -40 to 25 °C followed by OH protection in 67% overall yield. The preparation of **3** was achieved in 4 steps via reductive iodination[14] of monoprotected 2-butyne-1,4-diol to give **5** and its oxidation[15] followed by the Wittig olefination.[16] As suspected, all attempts to lithiate **3** with *t*-BuLi or *n*-BuLi led only to its decomposition presumably via β-elimination, which ruled out the employment of Protocols IIb and IIIb (Scheme 3). To employ Protocol IIa, acetalization of **2b** was carried out using ethylene glycol (10 equiv), TsOH (0.8%), molecular sieves 4A in benzene. However, the maximum yield of the desired cyclic acetal **6** was only 33% after several yield optimization attempts. While the exact course of the formation of a rather complex mixture is unclear, formation of some phenolic compounds is likely. Lithiation of **6** with *n*-BuLi at -78 °C, zincation with dry $ZnBr_2$ (0.5 equiv) at -78 to 25 °C, cross coupling with **3** using a 20% excess of **6** relative to **3** in the presence of 5 mol % of $Pd(PPh_3)_4$ in DMF at 25 °C for 6 h[7] did produce the desired cross-coupling product **7** in 77% yield, based on **3**, which was then treated with 10% aqueous oxalic acid absorbed on silica gel at 25 °C for 20 min[17] to give **8** in 62%. Removal of the TBDMS group with *n*-Bu_4NF provided nakienone B (**1**)[1]. Since this compound has not previously been characterized by spectroscopic means, it was further converted to the diacetate **1a**, (80% yield), whose ^{1}H and ^{13}C NMR are in excellent agreement with those reported in the literature.[1]



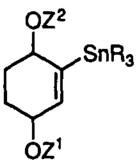
2b



6



7



11 (**a**: R = *n*-Bu, **b**: R = Me)

$Z^1 = SiMe_2Bu\text{-}t$

$Z^2 = SiMe_3$

The low-yield conversion of **2b** into **6** pointed to the desirability of developing a non-acidic synthetic protocol. To this end, **2a** was reduced with $NaBH_4$ and 0.4 *M* $CeCl_3 \cdot 7\ H_2O$ in MeOH[18] to give, after protection with Me_3SiCl and Et_3N, a 56/44 diasteromeric mixture of **9** in 95% yield. Using essentially the same conditions for both *in situ* generation of the alkenylzinc derivative and cross coupling as those for the conversion of **6** into **7**, the desired cross-coupling product **10** was obtained in 68% yield based on **3**. As before, a 20% excess of **9** relative to **3** was used. A detailed investigation of the metalation of **9** has indicated that the homo-Brook rearrangement[19] can be a serious side reaction but that it can be limited to the extent of 15% under the conditions indicated in Scheme 2. Further improvement may be achieved by using different silyl and other protecting groups, but this point remains to be investigated. Oxidation of **10** with the Swern reagent[15] provided an 89% yield of **8**, which was converted to **1** and **1a** as described above (Scheme 2). Thus, starting with a common intermediate **4**, the synthesis of **1** using the new protocol was achieved in 6 linear steps in about 20% yield which is roughly 4 times as high as that observed in the alternate 6-step conversion of **4** into **1** using Protocol IIa (~5% overall yield).

We also briefly attempted to compare relative efficiency of the three most frequently used metals in the Pd-catalyzed cross coupling, *i.e.*, Zn,[7,8,20] Sn,[9,21] and B,[22] in the new protocol. Conversion of **9** into both tri(*n*-butyl)stannyl and trimethylstannyl derivatives (**11a** and **11b**) was achieved in about 70% NMR yields in a manner similar to the genertion of the corresponding Zn reagent. However, attempts to couple either **11a** or **11b** with **3** under the conditions used in the literature[9,22] for alkenyl-alkenyl coupling, using 5 mol % of $Cl_2Pd(PhCN)_2$ or another Pd(II) or Pd(0) complex used in the literature,[9,21] $AsPh_3$ (0.1 equiv), and CuI (0.1 equiv) in *N*-methylpyrrolidinone, were unsuccessful, even though the same reagent system was satisfactory in coupling 2-iodo-2-cyclohexenone with phenyltributylstannane at 90 °C over 2 h in 74% yield by NMR. At 90 °C, the starting compounds **3** and **11** were consumed to give a complex mixture with no sign of cross coupling, while no reaction was observed at 60 °C over 12 h. A similar difficulty in the use of cyclohexenylstannanes has in fact been reported.[21b] We tentatively conclude that, even under extensively optimized conditions, the Pd-catalyzed coupling reaction of alkenylstannanes with alkenyl halides must be very much substrate dependent. Attempts to generate the boronic acid corresponding to **9** via its lithiation, boration with $B(OPr\text{-}i)_3$, and quenching with HCl in Et_2O[22b] led only to a rather complex mixture as judged by ^1H NMR spectroscopy. Consequently, no attempts to use this mixture for the desired cross coupling were made.

Further developments of chemo-, regio, and stereo-selective and -specific procedures for α-alkenylation of carbonyl compounds and their application to the synthesis of various natural products are in progress.

Acknowledgements. We thank the National Institutes of Health (GM36792) for support of this reasearch and Johnson-Matthey for a loan of $PdCl_2$. We also gratefully acknowledge information and data provided by Professor W. H. Gerwick.

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(*Received in USA* 9 *April* 1996; *revised* 7 *May* 1996; *accepted* 13 *May* 1996)