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Tetrahedron Letters 44 (2003) 4439–4442

TETRAHEDRON
LETTERS

Synthesis of tetrahydrofluorenes from the cycloadduct of 3-ethynyl-5-bromo-2-pyrone via cyclocarbopalladation reactions

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Received 3 April 2003; revised 17 April 2003; accepted 21 April 2003

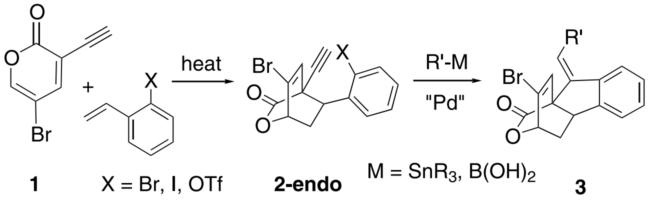
Abstract—Cycloadduct from 3-ethynyl-5-bromo-2-pyrone undergoes facile cyclocarbopalladation reactions to provide an array of polycarbocyclic compounds with a complete control of the olefin geometry. Both organotin and boron reagents can be used as a trapping anion source. Treatment of the resulting tetracycles with NaOMe gave rise to various tetrahydrofluorenes in good to excellent isolated yields. © 2003 Elsevier Science Ltd. All rights reserved.

The perhydrofluorene cores are the key feature of the steroid alkaloid type natural products including jerveratrum and cerveratrum, giberellic acid and its structural variants as well as kinamycin type antibiotics.[1]

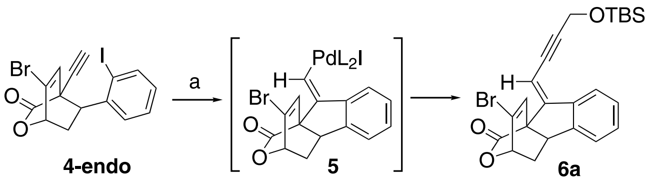
Recently, we have reported that 3,5-dibromo-2-pyrone undergoes regioselective Sonogashira coupling reactions at C3 position with various terminal alkynes to afford an array of 3-alkynyl-5-bromo-2-pyrones.[2] The resulting 3-alkynyl-5-bromo-2-pyrones exhibit potent ambident dienyl characters, proceeding facile Diels–Alder cycloadditions with either electron rich or poor dienophiles.[3] Cycloadducts with 2-halo-styrenes are of particular interest as they may be elaborated to furnish the polycarbocycle **3** via a carbopalladation/trapping process (cyclocarbopalladation) as illustrated below (Scheme 1).[4]

The alkyne and aryl halide group in the cycloadduct **2-*endo*** are positioned for immediate cross-addition of the aryl palladium species over the triple bond, upon initial oxidative addition of Pd(0) onto the aryl halide. Trapping of the resulting vinyl palladium with an anion would give rise to the polycarbocycle **3** which can be readily transformed into the tetrahydrofluorenes upon simple cleavage of the lactone bridge. Realizing the simplicity and efficiency of this process prompted us to investigate the above cyclocarbopalladation method on the cycloadducts of 3,5-dibromo-2-pyrone in detail.

Our initial attempts were made on the cycloadduct (**2-*endo***; X = Br) prepared from the cycloaddition of **1** with 2-bromo-styrene. No cyclization was observed, however, as the oxidative addition was much faster at the vinyl bromide than at the desired aryl bromide position. Replacement of the aryl bromine with iodine was thus made to enhance the reactivity at the aryl site. The Diels–Alder cycloaddition of 3,5-dibromo-2-pyrone with 2-iodo-styrene furnished the cycloadducts bearing iodine group at the aryl position as a mixture of *endo* and *exo* isomer (86:14) in 75% yield, after 6 h at 100°C in toluene. The reaction on the isolated **4-*endo*** using 1.2 equiv. of the alkynyl tin provided a mixture of the desired cyclic product **6a** in 45% isolated yield (Scheme 2), and a few byproducts (vide infra).



Scheme 1. D-A reaction and carbopalladation/anion capture.



(a) Bu_3Sn—≡—CH_2-OTBS/Pd(PPh_3)$_4$(10 mol%)/DMF/50 °C

Scheme 2. Cyclocarbopalladation of **4-*endo***.

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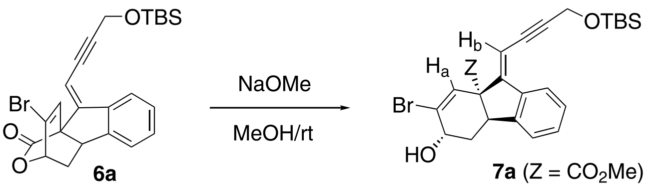
doi:10.1016/S0040-4039(03)01032-3

In this reaction sequence, the aryl palladium species generated after the initial oxidative addition of Pd(0) underwent the addition reaction across the triple bond in a *syn* fashion to provide the vinyl palladium intermediate **5** in an *E*-geometry.[4] The subsequent transmetalation and reductive elimination furnished the tetracyclic compound **6a**. The *E*-stereochemistry of the double bond was confirmed upon treatment with NaOMe in MeOH at rt. The resulting tetrahydrofluorene **7a**, produced in 85% yield, showed strong NOE between H_a and H_b (Scheme 3).

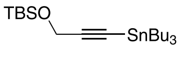
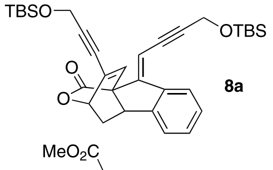
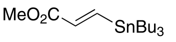
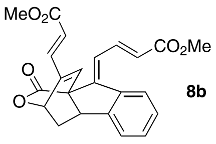
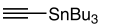
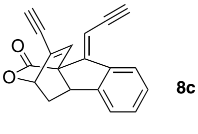
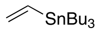
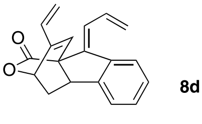
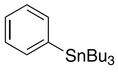
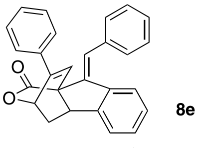
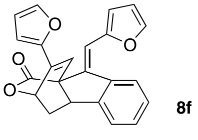
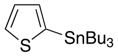
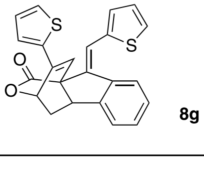


6a

7a (Z = CO_2Me)

Scheme 3. Lactone ring opening reaction with NaOMe.

Table 1. Trapping with various other stannanes

entry	stannane	time	product	yield
1		1 h	 **8a**	65%[a]
2		1 h	 **8b**	67%
3		0.5 h	 **8c**	71%
4		1 h	 **8d**	90%
5		6 h	 **8e**	trace
6		0.5 h	 **8f**	77%
7		1 h[a]	 **8g**	65%

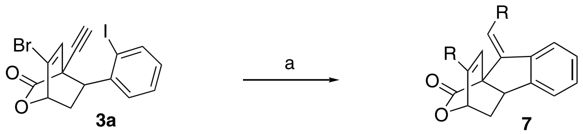
(a) Reaction condition: $Pd(PPh_3)_4$/DMF/50 °C

Major byproduct from the reaction (Scheme 2) was the one resulted from the additional coupling at the vinyl bromide group before and/or after the cyclization/trapping process.[5] Thus, we decided to use excess (3.0 equiv.) tin reagents to produce bis-coupling products directly, avoiding the complexity in the product isolation (Table 1). The reactions gave better results when heated at 100°C in toluene, except the entry 1 (due to thermal instability of the starting stannane).

A variety of organostannanes were effectively used, affording a series of functionally rich polycarbocyclic compounds in good to excellent isolated yields.[6] However, only trace of the cyclized products were formed when aryl stannanes were used (illustrated by the reaction with phenyl tin in entry 5). The steric hindrance of phenyl tributyltin may be accounted for the failure, by slowing down the transmetalation with the vinyl palladium species **5**.

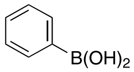
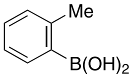
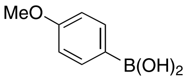
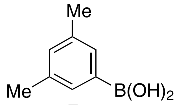
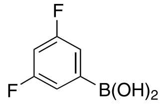
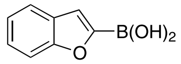
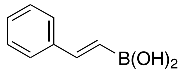
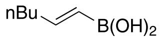
Trappings with aryl boronic acids gave much better results in those cases, as they are less sterically demand-

Table 2. Trapping with aryl and vinyl boronic acids



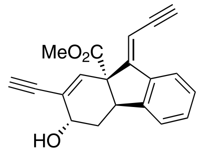
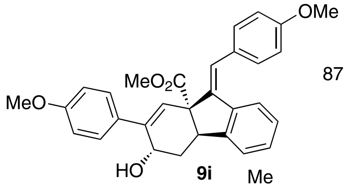
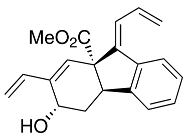
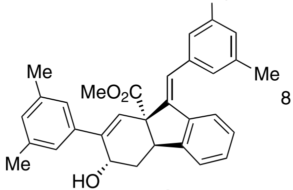
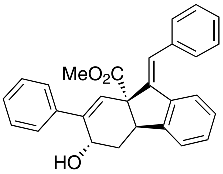
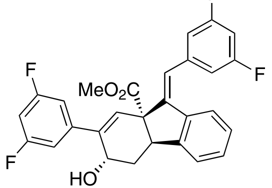
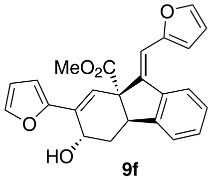
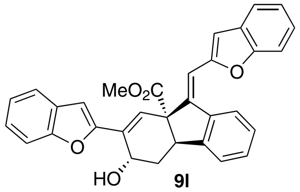
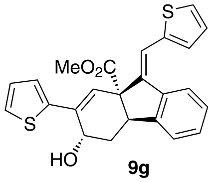
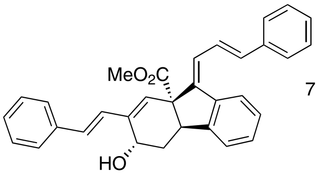
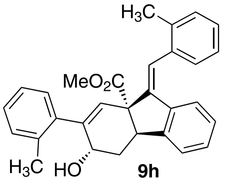
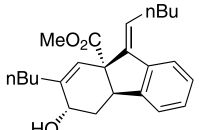
3a

7

entry	boronic acid	time	product	**yield**
1		0.5 h	**8e**	82%
2		0.5 h	**8h**	95%
3		10 min	**8i**	97%
4		2 h	**8j**	92%
5		1.5 h	**8k**	68%
6		1 h	**8l**	60%
7		1 h	**8m**	94%
8		1 h	**8n**	62%

(a) $R-B(OH)_2$ (3 eq.)/$Pd(PPh_3)_4$/$Na_2CO_3(aq)$/PhMe/100 °C

Table 3. Lactone ring opening reactions for the synthesis of tetrahydrofluorenes

entry	time	product	yield	entry	time	product	yield
1	30 min	 **9c**	50%	7	10 min	 **9i**	87%
2	30 min	 **9d**	65%	8	30 min	 **9j**	81%
3	30 min	 **9e**	70%	9	30 min	 **9k**	73%
4	10 min	 **9f**	92%	10	10 min	 **9l**	81%
5	10 min	 **9g**	50%	11	10 min	 **9m**	70%
6	30 min	 **9h**	61%	12	10 min	 **9n**	81%

ing. Again, we used excess boronic acids (3 equiv.) to avoid the formation of a mixture of mono- and di-substituted products (Table 2).[7]

When aryl boronic acid was used as a trapping agent, the cyclocarbopalladation turned out to be faster than the coupling at the vinyl bromide. Thus, the use of 1.2 equiv. of aryl boronic acid furnished mostly mono-substituted products, albeit not in an exclusive fashion. When vinyl boronic acid was used, however, the coupling at the vinyl bromide took place faster than the cyclocarbopalladation, thus providing bis-coupling products. The initially formed *endo*/*exo* cycloadducts need not be separated, as the corresponding *exo*-isomer cannot participate in this course of reaction due to the geometry of the alkyne and the aryl iodide groups. Lactone ring opening reactions of the resulting tetracyclic compounds with NaOMe in MeOH at rt provided the tetrahydrofluorenes **9e**–**9n** in fair to good isolated yields (Table 3).[8,9]

In summary, we have found that the cycloadduct prepared from the D-A cycloaddition of 3-alkynyl-5-bromo-2-pyrone with 2-iodo-styrene can undergo cyclocarbopalladation reactions to afford various functionalized polycarbocycles with complete control of the olefin geometry. Either organotin or boron reagent can be use as a trapping anion source. Sterically less demanding aryl boronic acids are much better trapping agents than tin counterparts. The resulting tetracycles are readily converted into the corresponding tetrahydrofluorenes upon cleavage of the lactone bridge with, for example in this study, NaOMe in MeOH.

Acknowledgements

This work was supported by the Korea Health 21 R&D Project, Ministry of Health & Welfare (01-PJ1-PG1-01CH03-0003) and BK21 Program.

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5. Lee, H.-S.; Kim, D.-S.; Won, H.; Choi, J. H.; Lee, H.; Cho, C.-G. *Tetrahedron Lett*. **2002**, *43*, 5591.
6. Representative procedure: To a sealed tube charged with **4** (50 mg, 0.1 mmol) were added $Pd(PPh_3)_4$ (10 mol%) and 130 mg (0.35 mmol) of tributylvinyltin dissolved in 1.0 mL of anhydrous toluene at rt. After 1 h at 100°C, the reaction mixture was concentrated and chromatographed (hexanes:EtOAc, 5:1) to furnish 29 mg of the product **8d** in 90% yield.
7. Representative procedure: To a sealed tube charged with **4** (50 mg, 0.1 mmol) were added $Pd(PPh_3)_4$ (10 mol%), 43 mg (0.35 mmol) of phenyl boronic acid dissolved in 1.0 mL of anhydrous toluene and 0.35 mL of aq. Na_2CO_3 (1 M) under Ar atmosphere at rt. After 1 h at 100°C, the reaction mixture was concentrated and chromatographed (hexanes:EtOAc, 5:1) to furnish 37 mg of the product **8e** in 82% yield.
8. Representative procedure: To a flask charged with 37 mg (0.1 mmol) of **8e** were added 1 mL of anhydrous MeOH and 0.07 mL of NaOMe (25% in MeOH) at rt. After 30 min at rt, the reaction mixture was partitioned into CH_2Cl_2 and H_2O. The separated organic solution was dried over $MgSO_4$, filtered, concentrated and chromatographed (hexanes:EtOAc, 5:1) to provide 28 mg of **9e** in 70% yield.
9. All the products were fully characterized with ^1H, ^{13}C NMR, FT-IR and HRMS.