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Synthesis of 2-Oxazolones and α-Aminoketones via Palladium-Catalyzed Reaction of β,β-Dibromoenamides

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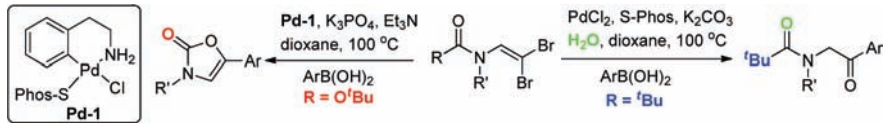
ABSTRACT



β,β-Dibromoenamides show two different interesting reactivities based on the choice of R group under the reaction conditions. On the basis of mechanistic studies, both reactions proceed via an intermolecular Suzuki−Miyaura C−C coupling and an intramolecular C−O coupling.

gem-Dihaloolefins have been important and versatile building blocks in palladium-catalyzed tandem reactions allowing the synthesis of ynamides, indoles, benzofurans, benzothiophenes, and other heterocycles.[1,2] However, nitrogen-substituted *gem*-dihaloolefins have received less attention in this class of transformation. A growing interest in the synthesis of nitrogen-containing cyclic and acyclic systems is relevant in the fields of chemistry, biochemistry, pharmaceutical science, and material science.[3]

Herein, we describe the development of new reactivity of β,β-dibromoenamides to generate 2-oxazolones and α-aminoketones. Interest in 2-oxazolones[4] and α-aminoketones[5] has recently grown, owing to their pharmacological activities and as important intermediates in organic synthesis.

Cossy first reported the intermolecular Suzuki coupling of β,β-dibromoenamides[6] with boronic acids using $Pd(PPh_3)_4$ as catalyst to give trisubstituted alkenes,[5a] but not via a tandem process. We initially considered that β,β-dibromoenamides **1** and **2** would lead to interesting nitrogen-containing heterocyclic compounds such as 3-substituted indoles **3** via double participation of the carbamate (R = O^{t}Bu) or amide (R = ^{t}Bu) group. Interestingly, we could observe the formation of compound **4** and **5** from **1** and **2**, respectively[7] (Scheme 1).

We initially assessed catalyst activity by conducting the coupling of β,β-dibromoenamide **1a** with phenylboronic acid. After varying several parameters, we found that a Buchwald's

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(6) For synthesis of dihalovinylamine, see: (a) Couty, S.; Barbazanges, M.; Meyer, C.; Cossy, J. *Synlett* **2005**, *6*, 905. (b) Brückner, D. *Tetetrahedron* **2006**, *62*, 3809.

(7) The *gem*-dibromination of formamides only works when an *N*-carbonyl protecting group on the formamide is present. Thus, β,β-dibromoenamides having a Boc or Piv group can be prepared. However, attempts to react other carbonyl protecting groups such as methylformyl (−COOMe) or benzoyl groups failed.

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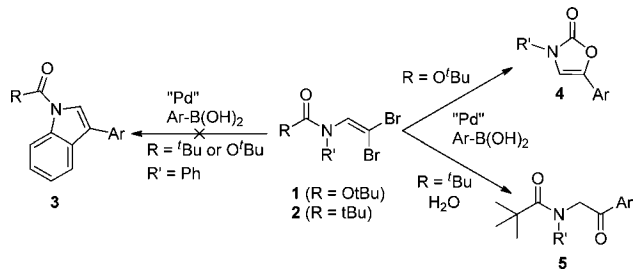
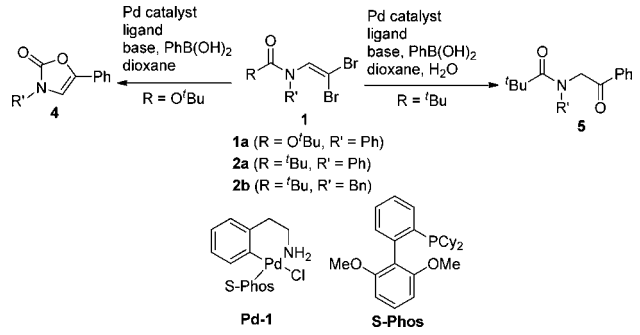
Scheme 1. Reactivity of *gem*-Dibromovinyl Systems



catalyst **Pd-1**[8] in dioxane at 100 °C with K_3PO_4/Et_3N as bases formed 2-oxazolone **4a** in good yield in 12 h (Table 1, entry 4).

Table 1. Initial Observations



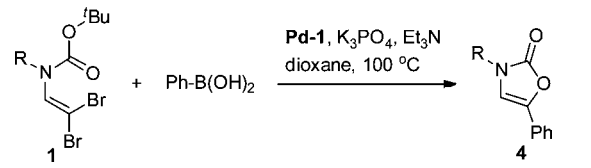
entry[a]	starting material	Pd/ligand	base	product	yield[b] (%)
1	**1a**	$Pd(OAc)_2$/S-Phos	K_2CO_3	**4a**	trace
2	**1a**	$Pd(OAc)_2$/S-Phos	K_3PO_4/Et_3N	**4a**	45
3	**1a**	$PdCl_2$/S-Phos	K_3PO_4/Et_3N	**4a**	61
4	**1a**	**Pd-1**	K_3PO_4/Et_3N	**4a**	80
5	**2a**	**Pd-1**	K_3PO_4/Et_3N	**5a**	–[c]
6	**2b**	**Pd-1**	K_3PO_4/Et_3N	**5b**	55
7	**2b**	$PdCl_2$/S-Phos	K_2CO_3	**5b**	72

[a] Reactions were conducted with **1** (0.15 mmol), boronic acid (0.225 mmol), palladium (6 mol %), ligand (12 mol %), base (0.45 mmol), Et_3N (0.05 mL, if applicable), dioxane (4 mL for **3** or 2 mL for **4**), and water (0.3 mmol, if applicable) at 100 °C for 14 h. [b] Isolated yield. [c] 30% conversion.

However, the coupling of β,β-dibromoenamide **2a** under the same reaction conditions provided <30% conversion to compound **5a** (Table 1, entry 5). On the other hand, the coupling of the β,β-dibromoenamide **2b** possessing a benzyl group provided the aminoketone **5b** in moderate yield. We found that a combination of $PdCl_2$ and S-Phos allowed an efficient synthesis of the α-aminoketone **5b** with K_2CO_3 as base (Table 1, entry 7). In both cases, reactions without boronic acids sometimes showed a trace amount of akynes, when employing stronger bases such as KO^{t}Bu.

Reactions of a series of β,β-dibromoenamide **1** and boronic acids were examined under the optimized conditions (Tables 2 and 3). Both alkyl and aromatic substituents on nitrogen were tolerated under these conditions. However, the electron-poor amine system **1c** was ineffective in this reaction,

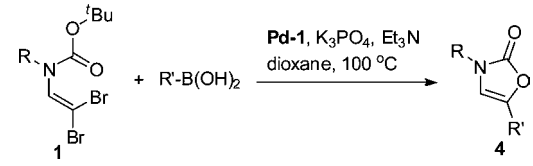
Table 2. Reaction Scope of Pd-Catalyzed Oxazolone Synthesis Varying Substituents on **1**



entry[a]	starting material	product	yield (%)[b]
1	**1a** (R = Ph)	**4a**	80
2	**1b** (R = Bn)	**4b**	80[c]
3	**1c** (R = 4-CF_3(C_6H_4)	**4c**	–[c]
4	**1d** (R = 4-MeO(C_6H_4))	**4d**	75[c]
5	**1e** (R = Me)	**4e**	54[c]
6	**1f** (R = -$(CH_2)_2$Ph)	**4f**	66[c]
7	**1g** (R = 2-F(Bn))	**4g**	82[c]
8	**1h** (R = cyclohexyl)	**4h**	94[d]
9	**1i** (R = CH(CH_3)Ph)	**4i**	91[d,e]

[a] Reactions were conducted with **1** (0.3 mmol), boronic acid (0.45 mmol), palladium (6 mol %), K_3PO_4 (0.6 mmol), Et_3N (0.1 mL), and dioxane (8 mL) at 100 °C for 14 h. [b] Isolated yield. [c] Identical result obtained with either 1.5 or 3 equiv of phenylboronic acid. [d] 3 equiv of boronic acids was used. [e] Chiral **1i** with 98% ee provided **4ie** in 98% ee.

Table 3. Reaction Scope of Pd-Catalyzed Oxazolone Synthesis Varying Boronic Acids



entry[a]	starting material	R′	product	yield (%)[b]
1	**1b** (R = Bn)	Ph	**4b**	80[c]
2	**1b**	2-Me(C_6H_4)	**4ba**	50
3	**1b**	3-Me(C_6H_4)	**4bb**	56
4	**1b**	4-Me(C_6H_4)	**4bc**	65
5	**1b**	4-F(C_6H_4)	**4bd**	50
6	**1b**	4-MeO(C_6H_4)	**4be**	41
7	**1i** (R = CH(CH_3)Ph)	Ph	**4i**	91[d,e]
8	**1i**	2-Me(C_6H_4)	**4ia**	84[d]
9	**1i**	2,6-diMe(C_6H_3)	**4ib**	25[d]
10	**1i**	4-Me(C_6H_4)	**4ic**	80[d]
11	**1i**	4-F(C_6H_4)	**4id**	75[d]
12	**1i**	4-OMe(C_6H_4)	**4ie**	72[d]
13	**1i**	(*E*)-2-styryl	**4if**	49[d,f]
14	**1i**	3-thienyl	**4ig**	87[d]
15	**1i**	2-MeO(C_6H_4)	**4ih**	73[d]
16	**1i**	4-CF_3(C_6H_4)	**4ii**	76[d]
17	**1i**	3-Cl(C_6H_4)	**4ij**	86[d]

[a] Reactions were conducted with **1** (0.3 mmol), boronic acid (0.45 mmol), palladium (6 mol %), K_3PO_4 (0.6 mmol), Et_3N (0.1 mL), and dioxane (8 mL) at 100 °C for 14 h. [b] Isolated yield. [c] Identical result obtained with either 1.5 or 3 equiv of phenylboronic acid. [d] 3 equiv of boronic acids was used. [e] Chiral **1i** with 98% ee provided **4ie** in 98% ee. [f] 46% of bis-Suzuki coupling product **4if′** isolated.

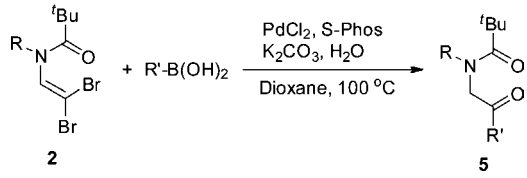
(8) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

providing evidence that the cyclization requires the electron-rich carbamate functional group, presumably due to its high nucleophilicity (Table 2, entry 3). Excellent yields were obtained with increasing steric hindrance (Table 2, entries 2, 5, 8, and 9), presumably because the carbon-bearing bromines and the carbamate group become closer by steric interactions between the R group and the O^{t}Bu group. However, reactions with sterically hindered substrates required excess boronic acids in order to achieve full conversion (Table 2, entries 13 and 14).

A variety of electron-rich, electron-poor, and sterically hindered boronic acids were also effective under the optimized conditions (Table 3). It is worth noting that the chiral substrate **1i** can be used in this transformation without stereochemical scrambling at the chiral center (Table 3, entry 7).

We probed the scope of the reactions using substrate **2**. Once again, electron -rich, electron-poor, and sterically hindered boronic acids coupled under the optimized conditions (Table 4, entries 4−13, see the Supporting Information for an X-ray crystal structure of **5b**). However, unlike the reactions of **1**, no ketone products were observed when aryl-substituted (Table 4, entries 1, 2, and 3) or sterically hindered substrates were employed (Table 4, entry 19). We hypothesized that the ketone formation proceeds by a participation of the amide carbonyl group. Steric minimization between the large R group and the ^{t}Bu group in **2h** seems to favor a conformation in which the amide oxygen points away from the reactive dibromide side. This conformation significantly inhibits the reaction due to the restricted amide group participation (Table 4, entry 19).

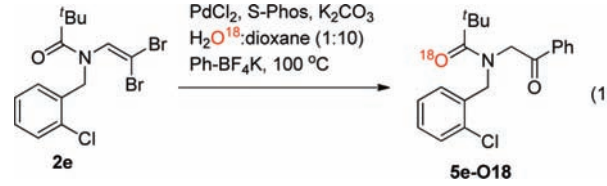
Table 4. Reaction Scope of α-Aminoketone Synthesis



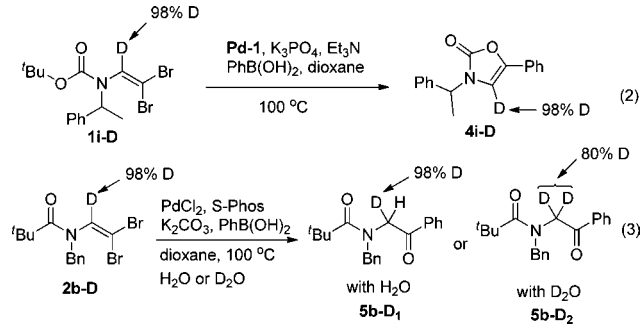
entry[a]	starting material	R′	product	yield (%)[b]
1	**2a** (R = Ph)	Ph	**5a**	–[c]
2	**2a′** (R = 4-OMe(C_6H_4))	Ph	**5a′**	–[c]
3	**2a″** (R = 4-NO_2(C_6H_4))	Ph	**5a″**	–[c]
4	**2b** (R = Bn)	Ph	**5b**	72
5	**2b**	2-Me(C_6H_4)	**5ba**	50
6	**2b**	3-Me(C_6H_4)	**5bb**	53
7	**2b**	4-Me(C_6H_4)	**5bc**	74
8	**2b**	2-Cl(C_6H_4)	**5bd**	36
9	**2b**	4-F(C_6H_4)	**5be**	61
10	**2b**	2-F,4-Me(C_6H_3)	**5bf**	50
11	**2b**	4-MeO(C_6H_4)	**5bg**	75
12	**2b**	3-TMS(C_6H_4)	**5bh**	40
13	**2b**	3-thienyl	**5bi**	57
14	**2c** (R = Me)	Ph	**5c**	57
15	**2d** (R = 2-F(C_6H_4)CH_2)	Ph	**5d**	83
16	**2e** (R = 2-Cl(C_6H_4)CH_2)	Ph	**5e**	65
17	**2f** (CH_2CH_2Ph)	Ph	**5f**	65
18	**2g** (CH_2CH_2COOEt)	Ph	**5g**	85
19	**2h** (CH(CH_3)Ph)	Ph	**5h**	–[c]

[a] Reactions were conducted with **2** (0.3 mmol), boronic acid (0.45 mmol), $PdCl_2$ (6 mol %), S-Phos (12 mol %), K_2CO_3 (0.9 mmol), H_2O (2 − 3 equiv), and dioxane (4 mL) at 100 °C for 14 h. [b] Isolated yield. [c] Starting material recovered.

To explore if the amide participates in the reaction, we performed an ^{18}O-labeling experiment (eq 1). When the reaction between **2e** and potassium phenyl-tetrafluoroborate salt was conducted in H_2O^{18}/dioxane (1:10), ^{18}O was found in the amide carbonyl group as clearly identified by IR analysis (1604.8 cm^{-1} (C═O^{18}) vs 1635.7 cm^{-1} (C═O^{16}), see the Supporting Information for IR data). This result supports participation[9] of the amide group during the reaction, presumably through a cyclic oxo-palladium intermediate.



To study the mechanism further, **1i-D** and **2b-D** were subjected to each of the reaction conditions (eqs 2 and 3). The experiments gave **4i-D** and **5b-D$_1$** each with 98% deuterium incorporated. These results eliminate the alkyne from the reaction pathway.[10] Interestingly, the use of D_2O for the coupling of **2b-D** and phenylboronic acid resulted in deuterium incorporation up to 80% (eq 3).



A number of experiments were planned to elucidate the order of coupling by subjecting potential intermediates **6** and **7** to the reaction conditions (Figure 1). Unfortunately, these intermediates could not be prepared by a variety of synthetic procedures.

Initial *cis*-activation of **2** (R = ^{t}Bu) could lead to acyl bromides **9**, which decompose to the corresponding carboxylic acids (Figure 1). Since the carboxylic acids were not observed during the reactions, the intermediate **9** (Figure

(9) Momiyama, N.; Kanan, M. W.; Liu, D. R. *J. Am. Chem. Soc.* **2007**, *129*, 2230.

(10) The product **5-bD$_1$** can undergo H/D exchange under the reaction conditions. If H/D exchange happens, it is probably not possible to get 98% D on **5b-D$_1$**. In fact, reaction of **5b** with 2 equiv of D_2O did not undergo H/D exchange under the reaction conditions.

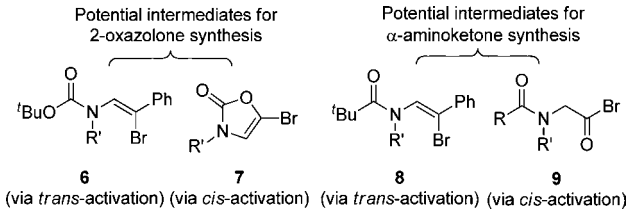
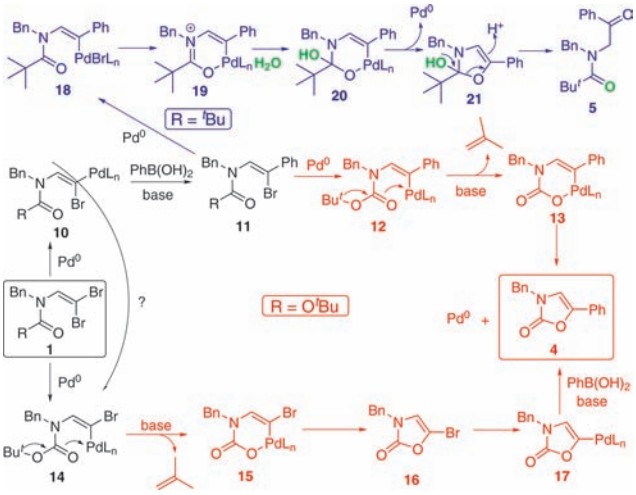


Figure 1. Potential intermeidates for 2-oxazolone and α-aminoketone synthesis.

1) does not appear on the reaction pathway for α-aminoketone synthesis.

The proposed mechanisms for 2-oxazolone and α-aminoketone synthesis are illustrated in Scheme 2. Pd(0) first undergoes oxidative addition into the trans-C−Br bond of **1**.[11] The resulting intermediate **10** couples with boronic acid to give the intermediate **11** (R = O^{t}Bu), which transforms into the oxopalladium complex **13** via **12**. This intermediate **13** subsequently undergoes reductive C−O coupling to give the final 2-oxazolone product **4**. Alternatively, cis-oxidative addition of compound **1** or the cis−trans isomerization[12] of **10** to **14** and subsequent C−O coupling results in 4-bromo-2-oxazolone **16**, which undergoes the Suzuki−Miyaura coupling to provide the final product **4**.

Scheme 2. Proposed Mechanisms



However, if R = ^{t}Bu on **1**, the complex **18**, which is obtained from oxidative addition to **11** (R = ^{t}Bu), transforms into the cationic oxo-palladium species **19**. This cationic complex **19** provides an intermediate **20** via nucleophilic attack of water. Finally, reductive elimination of this intermediate **20** provides compound **5** by decomposition[13] of the amide hemiacetal **21**, followed by protonation.

In summary, we have described a general and efficient method for the synthesis of 2-oxazolones and α-aminoketones from *β*,*β*-dibromoenamides and boronic acids using a Pd(0) catalyst. The results of the mechanistic studies for the 2-oxazolone synthesis showed two possible pathways (trans- and cis-activation), but those for the α-aminoketone synthesis revealed one pathway in which the amide oxygen is transferred to the vinyl group, later becoming the ketone functional group. Thus, both reactions proceed via the intermolecular Suzuki−Miyaura coupling/intramolecular C−O coupling. These findings reveal *cis*-bromo-*N*-vinylamines **11** as precursors for cyclic oxopalladium intermediates such as **13** and **20** that can undergo intramolecular C−O coupling.

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Supporting Information Available: Experimental procedures and spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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

(12) While two signals at 46.8 and 52.5 ppm (^{31}P NMR) were initially observed in 1:1 ratio at 60 °C, the signal at 46.8 ppm slowly disappeared. We believe that these two signals correspond to *trans*- and *cis*-vinylpalladium **10** and **14**. See the Supporting Information for details.

(13) For hydrolysis of cyclic amide hemiacetals, see: (a) Marinelli, E. R.; Johnson, F.; Iden, C. R.; Yu, P. L. I. *Chem. Res. Toxicol.* **1990**, *3*, 49. (b) Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9.