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Control of Chemoselectivity by Counteranions of Cationic Palladium Complexes: A Convenient Enantioselective Synthesis of Dihydrocoumarins

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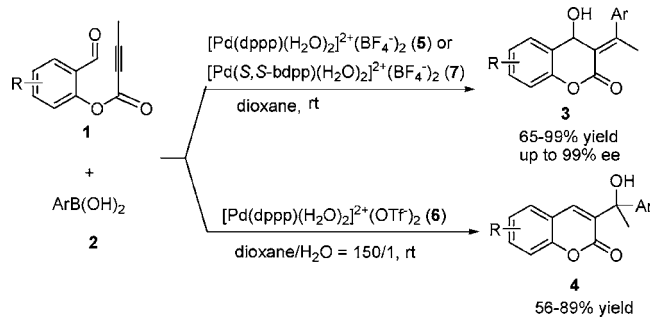
ABSTRACT



High chemoselectivity for the synthesis of two kinds of substituted coumarins controlled by the counteranions of the cationic palladium catalysts is described. The asymmetric version of the reaction for the synthesis of 3-alkylidene dihydrocoumarins is realized with high enantioselectivity.

Transition-metal-catalyzed tandem reactions provide efficient and powerful methods for the synthesis of carbo- and heterocyclic molecules.[1] Several examples of rhodium or palladium complex catalyzed tandem reactions of arylboronic acids and alkynals (or alkynones) to give hydroxy group substituted five- or six-membered rings have been described.[2]

Recently, our group focused on exploiting reactions using cationic palladium complexes to catalyze addition reactions to carbon−heteroatom multiple bonds.[2f,3] Inspired by the results of the above reactions, 2-formylaryl but-2-ynoate and arylboronic acids were chosen as the substrates to synthesize coumarin derivatives. The coumarin moiety is an important and central structural unit present in various biologically

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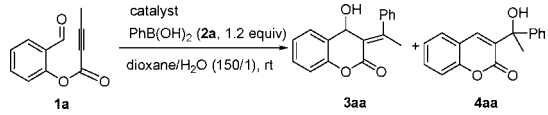
active compounds and also widely used as an intermediate in organic synthesis.[4] Many works about the synthesis of coumarins have been reported.[5] Among them, only a few examples were related to the synthesis of the optically active coumarins.[6] Herein, we report a mild and efficient way for the synthesis of 3-substituted coumarins and optically active 3,4-dihydrocoumarins chemoselectively using cationic palladium complexes with different counteranions.

In our initial investigation, alkynal **1a** was used as a model substrate in combination with $PhB(OH)_2$ to examine the effect of a variety of cationic palladium complexes as catalysts. Catalysts $Pd(CF_3CO_2)_2$/dppp and $[(bpy)Pd^{+}(\mu-OH)]_2(OTf^{-})_2$[3b,7] failed to give any products. When the cationic palladium complexes with dppp as the ligand were used as the catalysts, the reactions can proceed smoothly at room temperature, affording the expected product dihydrocoumarin **3aa** in excellent yields (Table 1, entries 1−3 and 5). It is surprising that the counteranions of the two cationic palladium complexes have great influence on the reactivity and chemoselectivity. The reaction catalyzed by $[Pd(dppp)(H_2O)_2]^{2+}(BF_4^{-})_2$ (**5**)[8] was completed within a much shorter time and was not influenced by the addition of a small amount of water as compared with that of $[Pd(dppp)(H_2O)_2]^{2+}(OTf^{-})_2$ (**6**)[9] (Table 1, compare entries 1 and 2 with 4−6). Another important difference in chemoselectivity between these two catalysts lies in that **6** can lead to the isomerization of **3aa** to coumarin **4aa** at room temperature with prolonged time (Table 1, entries 7 and 8), but **5** cannot (Table 1, entry 3).

Table 1. Effect of Catalysts in the Reaction of **1a** and Phenylboronic Acid[a]

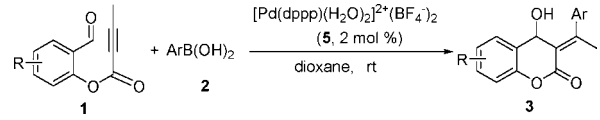


entry	catalyst	time (h)	yield (%)[b] 3aa	yield (%)[b] 4aa
1	**5**	0.33	98	0
2[c]	**5**	0.25	98	0
3[c]	**5**	60	96	trace
4	**6**	0.5	trace	0
5	**6**	40	93	trace
6[c]	**6**	40	61	trace
7	**6**	60	40	45
8	**6**	72	trace	75

[a] Reaction conditions: **1a** (0.15 mmol), $PhB(OH)_2$ (**2a**, 0.18 mmol, 1.2 equiv), and catalyst (2 mol %) were stirred in the solvent (3 mL, dioxane/H_2O = 150/1) at room temperature. [b] Isolated yield. [c] The solvent was dioxane.

Thus, 3-alkylidenedihydrocoumarins (**3**) or 3-substituted coumarins (**4**) can be synthesized from the same substrates by selecting one of the two catalysts. The results were summarized in Tables 2 and 3. The catalytic reaction worked well with a variety of arylboronic acids and 2-formylaryl but-2-ynoates. In the reaction catalyzed by **5**, 3-alkylidenedihydrocoumarins **3aa**−**3ea** can be obtained in good yields within 15−120 min at room temperature (Table 2). The stereochemistry of the exocyclic double bond was assigned

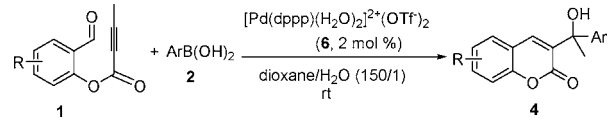
Table 2. Synthesis of Dihydrocoumarins **3** Catalyzed by **5**[a]



entry	R	Ar	time (min)	3	yield (%)[b]
1	H (**1a**)	Ph (**2a**)	15	**3aa**	98
2	H (**1a**)	*p*-MeC_6H_4 (**2b**)	30	**3ab**	83
3	H (**1a**)	*p*-FC_6H_4 (**2c**)	40	**3ac**	91
4	H (**1a**)	*p*-ClC_6H_4 (**2d**)	30	**3ad**	97
5	H (**1a**)	*p*-$^{i}PrC_6H_4$ (**2e**)	120	**3ae**	83
6	H (**1a**)	*p*-PhC_6H_4 (**2f**)	50	**3af**	92
7	H (**1a**)	*m*-ClC_6H_4 (**2g**)	10	**3ag**	99
8	H (**1a**)	*m*-MeC_6H_4 (**2h**)	50	**3ah**	93
9	H (**1a**)	*β*-naphthyl (**2i**)	40	**3ai**	99
10	4-Me (**1b**)	Ph (**2a**)	30	**3ba**	98
11	4-Cl (**1c**)	Ph (**2a**)	40	**3ca**	99
12	4-Br (**1d**)	Ph (**2a**)	25	**3da**	96
13[c]	(**1e**)[d]	Ph (**2a**)	70	**3ea**	81

[a] Reaction conditions: **1** (0.15 mmol), $ArB(OH)_2$ (**2**, 0.18 mmol, 1.2 equiv), and catalyst (**5**, 2 mol %) were stirred in dioxane (3 mL) at room temperature. [b] Isolated yield. [c] 1 mol % of the catalyst was used. [d] The substrate **1e** was 1-formyl-*β*-naphthyl but-2′-ynoate.

Table 3. Synthesis of **4** Catalyzed by **6**[a]



entry	R	Ar	time (h)	4	yield (%)[b]
1	H (**1a**)	Ph (**2a**)	72	**4aa**	75
2	H (**1a**)	*p*-MeC_6H_4 (**2b**)	72	**4ab**	74
3	H (**1a**)	*p*-FC_6H_4 (**2c**)	69	**4ac**	70
4	H (**1a**)	*p*-PhC_6H_4 (**2f**)	120	**4af**	73
5	H (**1a**)	*m*-MeC_6H_4 (**2h**)	64	**4ah**	64
6	H (**1a**)	*β*-naphthyl (**2i**)	33	**4ai**	89
7	H (**1a**)	*p*-$MeOC_6H_4$ (**2j**)	42	**4aj**	86
8	4-Me (**1b**)	Ph (**2a**)	120	**4ba**	88
9[c]	4-Cl (**1c**)	Ph (**2a**)	120	**4ca**	56
10[c]	4-Br (**1d**)	Ph (**2a**)	120	**4da**	60
11	(**1e**)[d]	Ph (**2a**)	70	**4ea**	74
12	6-MeO (**1f**)	Ph (**2a**)	88	**4fa**	63

[a] Reaction conditions: **1** (0.15 mmol), $ArB(OH)_2$ (**2**, 0.18 mmol, 1.2 equiv), and catalyst (2 mol %) were stirred in the solvent (3 mL, dioxane/H_2O = 150/1) at room temperature. [b] Isolated yield. [c] The reaction temperature was 40 °C. [d] The substrate **1e** was 1-formyl-*β*-naphthyl but-2′-ynoate.

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as (*E*)-configuration based on X-ray crystallography of product **3ab**. On the other hand, 3-substituted coumarins **4aa**−**4fa** (the structure of **4aa** was confirmed by X-ray crystallography) can also be obtained in moderate to good yields under the catalysis of **6** within a longer time (33−120 h, Table 3).

Subsequently, the asymmetric version of this cyclization reaction was studied. We first tried to test the reaction by using chiral bisphosphines as ligands. To simplify the experimental procedure, $Pd(CH_3CN)_4(BF_4)_2$ (2 mol %)/ligand (2.2 mol %) was used to perform the asymmetric reactions for substrates **1a** and $PhB(OH)_2$. To our delight, in the presence of $Pd(CH_3CN)_4(BF_4)_2$ and (*S*,*S*)-bdpp, dihydrocoumarin **3aa** can be afforded in moderate yield with 93% ee value despite that most of the ligands ((*R*)-binap, (*S*)-S1 and (*S*)-S2 as shown in Figure 1) tried were

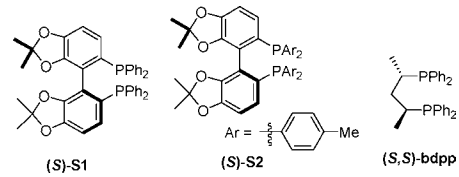

Figure 1. Chiral ligands used.

ineffective. However, the time (18 h; Table 4, entry 1) required for this catalytic asymmetric reaction was much longer than that catalyzed by **5** (15 min, Table 2, entry 1).

It was regarded that this time difference might be due to the two different types of catalysts (the presence or absence of CH_3CN). Thus, the catalyst $[Pd(S,S\text{-bdpp})(H_2O)_2]^{2+}(BF_4^-)_2$ (**7**) which has the similar structure with **5** was synthesized to perform the reaction again. It is exciting that the cyclization reaction was completed only in 20 min to give the product with good yield and high enantioselectivity at room temperature (99% yield, 95% ee, Table 4, entry 2). Under these mild conditions, a series of optically active

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(8) For the preparation of complex **5**, see Supporting Information.

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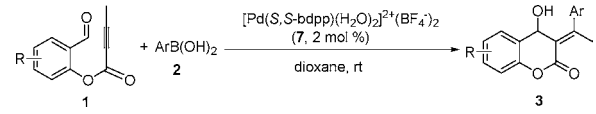
Table 4. Enantioselective Synthesis of **3** Catalyzed by **7**[a]



entry	1	2	time (min)	3	yield (%)[b]	ee (%)[c]
1[d]	**1a**	**2a**	1080	**3aa**	65	93 (+)
2	**1a**	**2a**	20	**3aa**	99	95 (+)
3	**1a**	**2b**	25	**3ab**	99	95 (+)
4	**1a**	**2c**	20	**3ac**	88	94 (+)
5	**1a**	**2d**	400	**3ad**	76	87 (+)
6	**1a**	**2e**	80	**3ae**	94	99 (+)
7	**1a**	**2f**	25	**3af**	99	96 (+)
8	**1a**	**2g**	40	**3ag**	99	95 (+)
9	**1a**	**2h**	60	**3ah**	93	94 (+)
10	**1a**	**2i**	40	**3ai**	99	93 (−)
11	**1b**	**2a**	40	**3ba**	75	91 (+)
12	**1c**	**2a**	50	**3ca**	97	95 (+)
13	**1d**	**2a**	30	**3da**	96	95 (+)
14	**1e**	**2a**	50	**3ea**	66	92 (+)

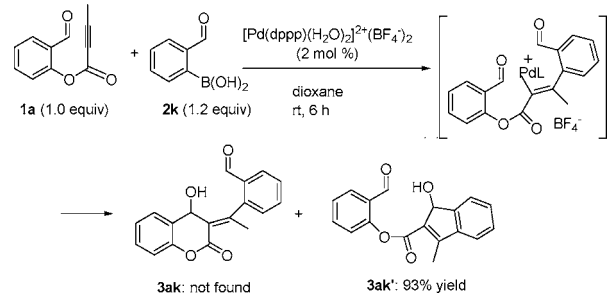
[a] The reaction conditions were similar to Table 2. [b] Isolated yield. [c] The ee values were determined by chiral HPLC. The sign of optical rotation was indicated in parentheses (for details see Supporting Information). [d] The catalyst was $Pd(CH_3CN)_4(BF_4)_2$ (2 mol %)/(*S*,*S*)-bdpp (2.2 mol %).

dihydrocoumarins **3** were synthesized in excellent yields with high enantioselectivity. The results were shown in Table 4.

Then we focused our efforts on establishing optimal conditions for the enantioselective formation of coumarin **4aa**. Similarly, $Pd(OTf)_2{\cdot}2H_2O$/ligand was chosen as the catalyst to test the reactions. Unfortunately, all of the chiral bisphosphines including (*R*)-binap and those listed in Figure 1 were not suitable, giving the product in very low yield with no enantioselectivity.

Next, a reaction using **1a** and 2-formylphenylboronic acid (**2k**) as the substrates was conducted in the presence of 2 mol % of $[Pd(dppp)(H_2O)_2]^{2+}(BF_4^-)_2$. The expected product **3ak** was not obtained, but a substituted indenol **3ak′** was produced similar to our reported work[3e] (Scheme 1). This

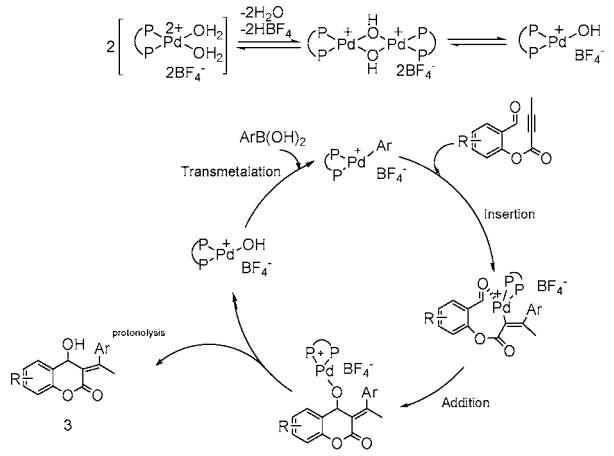
Scheme 1. Reaction of **1a** and **2k**



means that the vinylpalladium in the intermediate generated from carbopalladation of the alkyne in **1a** predominantly adds to the formyl group of **2k** to form an indenol. The structure of **3ak′** was confirmed by X-ray crystallography.

A plausible mechanism for this tandem reaction under the catalysis of $[Pd(dppp)(H_2O)_2]^{2+}(BF_4^-)_2$ (**5**) to produce dihydrocoumarins **3** is shown in Scheme 2, which involves

Scheme 2. Mechanism of the Formation of Dihydrocoumarins **3**



the tandem reactions of transmetalation of arylboronic acids with the palladium catalyst, carbopalladation of alkynoates, and the addition of vinylpalladium species to the aldehyde. In the case of using **6** as the catalyst, **3** may be formed first in a similar way, followed by isomerizing to coumarins **4** catalyzed by HOTf produced in situ from $[Pd(dppp)(H_2O)_2]^{2+}(OTf^-)_2$.[10] Thus, product **3aa** was stirred in the presence of a catalytic amount of HOTf or HBF_4. It was found that HOTf can lead to the isomerization of **3aa** to **4aa** in 6 h,[11] but HBF_4 cannot.

The reason for the difference in reactivity of these two cationic complexes (**5** and **6**) is not clear. Several papers reported that the difference in reactivity of the similar cationic complexes with these two counteranions is due to their coordinating ability to the transition metals, and BF_4^- is less coordinating than TfO^-.[12] Thus, catalyst **5** exhibits the more vacant site for coordinating with the substrates, making the reaction much easier to occur.

In summary, we have developed a new cationic palladium complex catalyzed cyclization reaction for the synthesis of substituted coumarins under very mild conditions. It is worth noting that counteranions in the catalysts have great influence on the reactivity and chemoselectiviy. Two kinds of coumarins can be obtained selectively by utilizing catalysts with different counteranions. The asymmetric version of the reaction using (*S*,*S*)-bdpp as the ligand to yield 3-alkylidenedihydrocoumarins was successful with high enantioselectivity. Further studies on the selectivity of catalysts with different counteranions are underway.

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Supporting Information Available: Experimental procedures, characterization data copies of NMR spectra of new compounds, HPLC data of optically active products, and CIF files of compounds **3ab**, **3ak′**, and **4aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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