JOC*Note*

Efficient Synthesis of Dibenzo[*a*,*c*]cyclohepten-5-ones via a Sequential Suzuki−Miyaura Coupling and Aldol Condensation Reaction

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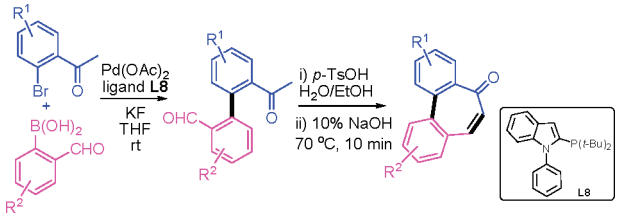

A common strategy for the synthesis of a 7-membered-ring system with a Suzuki−Miyaura coupling followed by an acid/base-promoted intramolecular aldol condensation reaction has been developed. The reaction of 2′-bromoacetophenones with 2-formylphenylboronic acids in the presence of $Pd(OAc)_2$ and CataCXium PIntB **L8** efficiently provided biaryl compounds, which were transformed to a wide array of dibenzo[*a*,*c*]cyclohepten-5-ones in excellent yields by a sequential treatment with *p*-TsOH, followed by 10% aq NaOH.

Colchicine (**1**), allocolchicine analogues (**2**−**5**), and metasequirine B (**6**) attract synthetic and medicinal chemists due to their remarkably unique structural features and interesting bioactive properties (Figure 1).[1,2] Of note, *N*-acetylcolchinol (**3**) and its prodrug ZD 6126 (**5**) exhibit highly potent anticancer effects via inhibition of tubulin polymerization.[3] The central

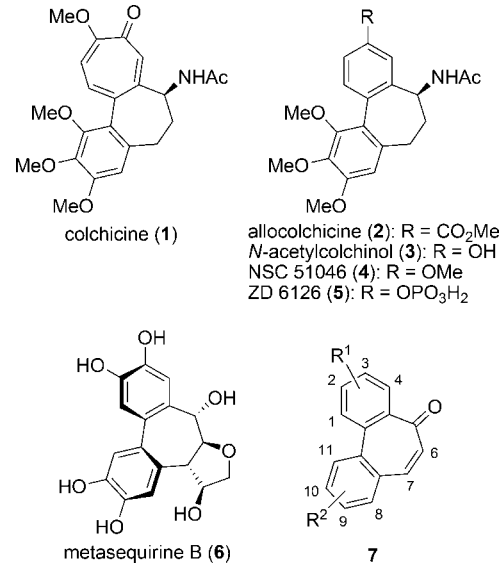

FIGURE 1. Colchicine, allocolchicine analogues, metasequirine B, and dibenzo[*a*,*c*]cyclohepten-5-one framework.

7-membered ring is generally known to play an important role in both stereochemistry and bioactivity. Various approaches toward the synthesis of allocolchicine analogues have been developed, including the transformation of natural colchicines,[4] the ring expansion of phenanthrene derivatives,[5] Diels−Alder reactions,[6] nonphenolic or phenolic biaryl oxidative couplings,[7] direct arylations,[8] and Nicolas reactions.[9] From a synthetic point of view, dibenzo[*a*,*c*]cyclohepten-5-one **7** represents a key intermediate en route to numerous allocolchicine analogues. Among the routes, a C−C coupling reaction followed by an aldol condensation would be the most attractive if high catalytic activities were realized.

At the outset of our studies, Leonard and co-workers at AstraZeneca had already published an elegant total synthesis of ZD6126 (**5**) that employed an Ullmann biaryl coupling reaction and aldol condensation sequence for the assembly of the cycloheptenone core.[10] Kocienski's group subsequently reported an enantioselective route to (−)-*N*-acetylcolchinol (**3**) that exploited a Suzuki−Miyaura coupling reaction/aldol condensation sequence for the construction of the 7-membered-

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(1) For reviews, see: (a) Capraro, H. G.; Brossi; A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, FL, 1984; Vol. 23, Chapter 1. (b) Boyé, O.; Brossi, A. In *The Alkaloids*; Brossi, A.; Cordell, G. A., Eds.; Academic Press: San Diego, CA, 1992; Vol. 41, p 125. (c) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3230–3256.

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SCHEME 1. Direct One-Pot Synthesis of Dibenzo[*a*,*c*]cyclohepten-5-one

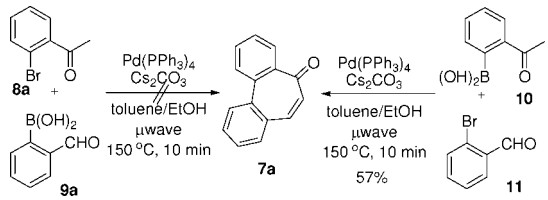
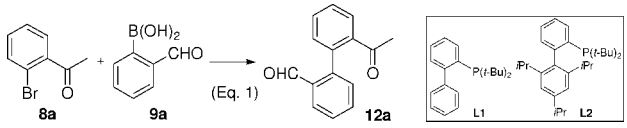


TABLE 1. Optimization of a Catalytic System for the Suzuki−Miyaura Coupling Reaction[a]



entry	Pd	ligand	base	solvents	time (h)	yield (%)[b]
1	$Pd(OAc)_2$	**L1**	KF	THF	2	92
2	$Pd(OAc)_2$	**L1**	K_3PO_4	THF	2	84
3	$Pd(OAc)_2$	**L1**	CsF	THF	2	81
4	$Pd(OAc)_2$	**L1**	Cs_2CO_3	THF	2	0
5	$Pd(PPh_3)_4$	**L1**	KF	THF	24	16
6	$PdCl_2$	**L1**	KF	THF	24	36
7	$Pd_2(dba)_3$	**L1**	KF	THF	24	70
8	$Pd(OAc)_2$	**L1**	KF	dioxane	2	87
9	$Pd(OAc)_2$	**L2**	KF	THF	2	65

[a] Reaction conditions: **8a** (0.5 mmol), **9a** (0.75 mmol, 1.5 equiv), Pd (2.0 mol %), base (1.5 mmol, 3 equiv), ligand (4.0 mol %), solvent (1.5 mL), rt. [b] Isolated yield.

ring moiety.[11] However, the need remains for the development of novel catalytic systems that enhance the reaction yields while maintaining rapid access to a wide range of derivatives.

As part of our ongoing research into the chemistry of polycycles, we recently reported a direct, one-pot method for the synthesis of phenanthrenes via a Suzuki−Miyaura coupling/aldol condensation cascade.[12] In addition, the application of this method to pharmacologically important aristolactam analogues was explored.[13] Herein, we have extended the scope of this protocol to include the more formidable 7-membered-ring systems, such as dibenzo[*a*,*c*]cyclohepten-5-one.

In the first instance, we employed a standard one-pot protocol, which was explored by our laboratory.[12,13] Initial attempts at the one-pot reaction of bromoacetophenone **8a** with formylphenylboronic acid **9a** were unsuccessful (Scheme 1). Alternatively, switching the coupling partners to aryl bromide **11** and boronic acid **10** led to the formation of the desired product, **7a**, in 57% yield. With this promising result in hand, we underwent considerable efforts to find a suitable catalytic system for the one-pot Suzuki−Miyaura coupling/aldol condensation reaction cascade. We, however, were faced with the inefficacy of the one-pot procedure. At that point, we believed that the challenge lie in the Suzuki−Miyaura coupling reaction, due to the presence of the less tolerant *o*-acetyl moiety, presumably via formation of a stable palladacyclic structure.[14] Consequently, our attention was turned to the stepwise reaction such that relatively milder reaction conditions could be applied.

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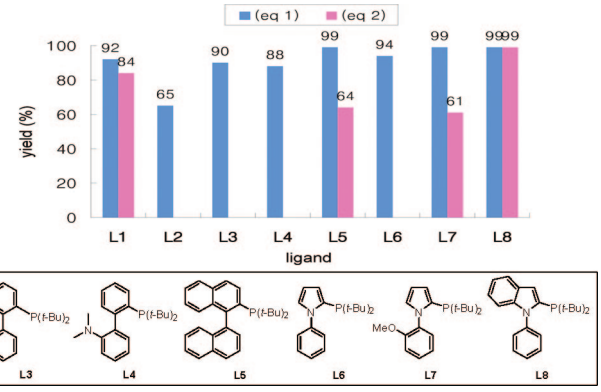
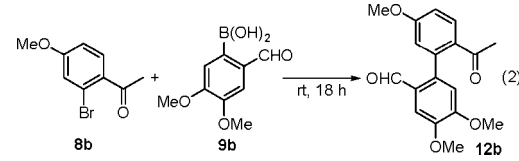


FIGURE 2. Ligand effect on the Suzuki−Miyaura coupling reaction.

We first examined the Suzuki−Miyaura coupling reaction at room temperature, following the procedure described by Buchwald et al.[15] The results are illustrated in Table 1. The coupling of aryl bromide **8a** with boronic acid **9a** in the presence of JohnPhos **L1** and KF in THF proceeded in 92% yield (entry 1). In contrast, coupling between **10** and **11** was fruitless in giving biaryl **12a**. With K_3PO_4 or CsF as a base, the couplings were less effective and provided **12a** in 84% or 81% yield, respectively (entries 2 and 3). Surprisingly, the use of Cs_2CO_3 appeared to inhibit catalytic turnover (entry 4). Variations on the palladium source ($Pd(PPh_3)_4$, $PdCl_2$, $Pd_2(dba)_3$) gave inferior yields, even with longer reaction times (entries 5−7). Changing the solvent to dioxane led to the formation of **12a** in 87% yield (entry 8). After screening a variety of ligands[16] while maintaining the best combinations of reaction conditions ($Pd(OAc)_2$, KF, and THF), we found that only ligand **L2** proved to be effective, furnishing **12a** in acceptable yield (entry 9). It is particularly noteworthy that ligands **L1** and **L2**, only possessing a di-*tert*-butyl phosphinyl group, readily facilitate the Suzuki−Miyaura coupling reaction, suggesting that the high catalytic activity may result from their ability to inhibit the formation of palladacycles.

With this result in mind, we next examined a broad range of Buchwald's biaryl phosphine ligands **L1**−**L5** and Beller's heteroarylphosphine ligands **L6**−**L8**, all bearing the di-*t*ert-butyl phosphine group (Figure 2). In the reaction of **8a** with **9a** (eq 1), all ligands provided **12a** in excellent yields. For further optimization of the ligand, the coupling of less reactive partners such as aryl halide **8b** and **9b** was carried out (eq 2). As shown in Figure 2, among the ligands tested (**L1**, **L5**, **L7**, and **L8**), CataCXium PIntB **L8** proved to be the most effective.[17] We believe that the efficacy of coupling reactions with ligand **L8** depends not only on the steric bulkiness but also on the electron richness. For example, ligands possessing the *tert*-butyl group led to the best results, while cyclohexyl-substituted phosphine ligands gave no or little desired coupling product.[18]



Having established suitable conditions, the scope and limitations of this protocol were explored. The results are summarized

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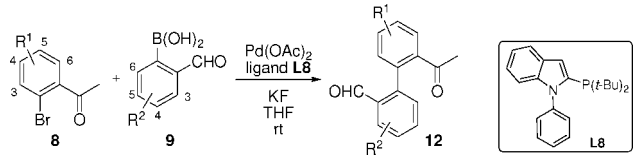
TABLE 2. Synthesis of Biaryl Keto-Aldehydes[a]

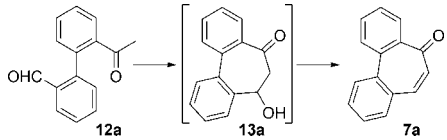


8 9 12

entry	R^1 (8)	R^2 (9)	time (h)	12	yield (%)[b]
1	H (**8a**)	H (**9a**)	2	**12a**	99
2	4-OMe (**8b**)	4,5-di-OMe (**9b**)	18	**12b**	99
3	H (**8a**)	4-Cl (**9c**)	2	**12c**	96
4	H (**8a**)	4-OMe (**9d**)	2	**12d**	94
5	H (**8a**)	4,5-OCH_2O- (**9e**)	2	**12e**	99
6	H (**8a**)	5-Me (**9f**)	2	**12f**	86
7	H (**8a**)	5-OMe (**9g**)	2	**12g**	74
8	H (**8a**)	 (**9h**)	22	**12h**	66
9	H (**8a**)	 (**9i**)	22	**12i**	34 (21)[c]
10	H (**8a**)	 (**9j**)	2	**12j**	92
11	4-OMe (**8b**)	H (**9a**)	18	**12k**	90
12	4-OMe (**8b**)	4-Cl (**9c**)	22	**12l**	60
13	4-F (**8c**)	H (**9a**)	2	**12m**	91
14	4-F (**8c**)	4,5-di-OMe (**9b**)	2	**12n**	99
15	4-F (**8c**)	4,5-OCH_2O- (**9e**)	2	**12o**	99
16	4-F (**8c**)	5-Me (**9f**)	2	**12p**	81
17	4,5-di-OMe (**8d**)	4,5-di-OMe (**9b**)	1[d]	**12q**	96

[a] Reaction conditions: **8** (0.5 mmol), **9** (0.75 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.0 mol %), KF (1.5 mmol, 3 equiv), **L8** (4.0 mol %), THF (1.5 mL), rt. [b] Isolated yield. [c] Isolated yield of **13i**. [d] The reaction was run at 80 °C.

TABLE 3. Optimization of Intramolecular Aldol Condensation Reaction



12a 13a 7a

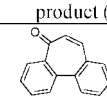
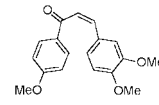
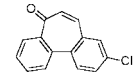
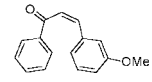
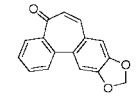
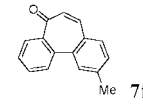
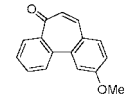
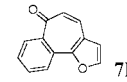
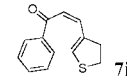
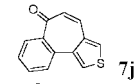
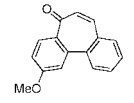
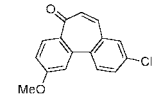
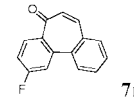
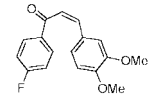
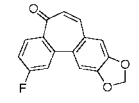
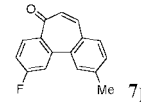
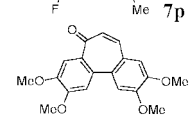
entry	conditions	yield (%)[a]
1	Cs_2CO_3 (3 equiv), toluene/EtOH = 2:1, microwave 150 °C, 10 min	trace
2	*p*-TsONa ("old", 20 mol %, pH 10.38[c]), H_2O/EtOH = 1:1, 70 °C, 2 h	87
3	*p*-TsONa ("new", 20 mol %, pH 9.00[c]), H_2O/EtOH = 1:1, 70 °C, 24 h	NR[b]
4	*p*-TsNa (20 mol %), H_2O/EtOH = 1:1, 70 °C, 24 h	NR[b]
5	(i) *p*-TsOH (20 mol %), H_2O/EtOH = 1:1, 1 min, and then (ii) 10% NaOH (40 mol %), 70 °C, 10 min	94
6	premixed *p*-TsOH (20 mol %) and 10% NaOH (40 mol %), H_2O/EtOH = 1:1, 70 °C, 1 h	70
7	10% NaOH (40 mol %), H_2O/EtOH = 1:1, 70 °C, 1 h	65

[a] Isolated yield. [b] No reaction. [c] pH value measured by a pH meter.

in Table 2. Couplings of **8a** with a wide variety of *o*-formylarylboronic acids **9a**,**c**−**g** smoothly proceeded to give the corresponding biaryl products **12a**,**c**−**g**, regardless of the nature of substituents on the aryl ring (entries 1 and 3−7). Heteroaryl-

(16) Other ligands (DavePhos, S-Phos, X-Phos, *rac*-BINAP, DPPF, DPEphos, and 2-(dicyclohexylphosphino)biphenyl) provided no or little desired product.

TABLE 4. Synthesis of Dibenzo[*a*,*c*]cyclohepten-5-ones[a]

entry	biaryl (12)	product (7)	yield (%)[b]
1	**12a**	 **7a**	94
2	**12b**	 **7b**	98
3	**12c**	 **7c**	89
4	**12d**	 **7d**	93
5	**12e**	 **7e**	93
6	**12f**	 **7f**	87
7	**12g**	 **7g**	93
8	**12h**	 **7h**	91
9	**12i**	 **7i**	93
10	**12j**	 **7j**	92
11	**12k**	 **7k**	90
12	**12l**	 **7l**	88
13	**12m**	 **7m**	93
14	**12n**	 **7n**	95
15	**12o**	 **7o**	93
16	**12p**	 **7p**	88
17	**12q**	 **7q**	96

[a] Reaction conditions: **12** (0.45 mmol), *p*-TsOH (20 mol %), H_2O/EtOH = 1 mL:1 mL, rt, 1 min, and then 10% aq NaOH (40 mol %), 70 °C, 10 min. [b] Isolated yield.

boronic acids **9h**−**j** also proved feasible, leading to the heteroaryl−aryl systems **12h**−**j** in reasonable to good yields

(entries 8−10). Interestingly, in the case of **9i**, the desired product **12i** was obtained in only 34% yield, along with an advanced aldol intermediate **13i** in 21% yield (entry 9). Reaction of the *p*-methoxy-substituted acetophenone **8b** proved difficult, presumably because of an increase in the electron density at the acetyl moiety favoring formation of the palladacycle. However, simply employing a longer reaction time afforded the desired products in good to excellent yields (entries 2, 11, and 12). When using *p*-fluoro-substituted acetophenone **8c** as the substrate, as expected, the reaction provided the coupling products in excellent yields (entries 13−16). In addition, the doubly deactivated substrate **8d** was also effective and afforded **12q** in 96% yield,[2] simply by heating the mixture at 80 °C for 1 h (entry 17).

Our next goal was the cyclization of biaryl keto-aldehydes via an aldol condensation under typical base-promoted conditions. However, it turned out to be difficult to obtain a satisfactory yield in this reaction. Following the literature method,[19] the addition of sodium *p*-toluenesulfonate led to the formation of the aldol adduct in high yield. During optimization of reaction conditions, however, a lack of reproducibility was observed. Through careful scrutiny as illustrated in Table 3, we realized that "old" sodium *p*-toluenesulfonate (which had been stored on a benchtop for quite a long period and changed to wet solid) afforded the desired product, whereas the "new" one provided no desired product (entry 2 vs. entry 3).[20] With sodium *p*-toluenesulfinate, no reaction was observed (entry 4). After a screening of a variety of conditions, we were pleased to find that the sequential treatment of keto-aldehyde **12a** with *p*-TsOH (20 mol %) and then 10% aq NaOH solution (40 mol %) at 70 °C for 10 min furnished the dibenzo[*a*,*c*]cyclohepten-5-one **7a** in 94% yield (entry 5). In this case, we reasoned that each of the aldol counterparts would be first activated by acid, and then dehydration of intermediate **13a** would be promoted by base.

Finally, biaryl keto-aldehydes can be further elaborated to dibenzo[*a*,*c*]cyclohepten-5-ones by using an acid/base-promoted intramolecualr aldol condensation. The results are illustrated in Table 4. All substrates possessing electron-donating or electron-withdrawing groups efficiently proceeded to provide the corresponding aldol adducts in excellent yields. It is notable that heteroaryl−aryl compounds **12h**−**j** also proved effective in affording the 7-membered-ring systems (**7h**−**j**) in a range of 91−93% yields (entries 8−10).

In summary, we have developed an efficient catalytic system for the synthesis of dibenzo[*a*,*c*]cyclohepten-5-ones via a Suzuki−Miyaura coupling in the presence of $Pd(OAc)_2$ and CataCXium PIntB **L8**, followed by an acid/base-promoted intramolecualr aldol condensation. Further study is now in progress for applications of this protocol toward the total synthesis of natural products as well as pharmaceuticals.

Experimental Section

General Procedure for the Suzuki−Miyaura Coupling Reaction. Acetophenone **8** (0.5 mmol), boronic acid **9** (0.75 mmol), $Pd(OAc)_2$ (2.2 mg, 2.0 mol %), KF (87 mg, 1.5 mmol), and **L8** (6.7 mg, 4.0 mol %) were sequentially added to an oven-dried microwave vial. The mixture was suspended in THF (1.5 mL) and stirred for 2 h at rt. The reaction mixture was directly purified by silica gel column chromatography (10% EtOAc/hexanes) to provide the corresponding biaryl keto-aldehyde **12**. Data for **12b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.83 (d, 1H, J = 8.7 Hz), 7.51 (s, 1H), 7.00 (dd, 1H, J = 8.7, 2.6 Hz), 6.78 (d, 1H, J = 2.6 Hz), 6.69 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 190.1, 161.4, 153.4, 149.0, 140.4, 139.5, 132.2, 131.6, 127.1, 117.8, 112.2, 108.5, 56.3, 56.1, 55.6, 29.3; HRMS (EI) calcd for $C_{18}H_{18}O_5$ [M^+] 314.1157, found 314.1157.

General Procedure for the Intramolecular Aldol Condensation. To a solution of biaryl keto-aldehyde **12** (0.446 mmol) in H_2O/EtOH (1 mL/1 mL) was added *p*-TsOH (17 mg, 0.089 mmol). The mixture was stirred at room temperature for 1 min, and then 10% aq NaOH solution (71 mg, 0.178 mmol) was added. After being stirred at 70 °C for 10 min, the resulting mixture was cooled to rt and diluted with water (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to provide dibenzo[*a*,*c*]cyclohepten-5-one **7**. Data for **7b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, 1H, J = 8.8 Hz), 7.35 (s, 1H), 7.34 (d, 1H, J = 3.9 Hz), 7.25 (d, 1H, J = 12.2 Hz), 7.11 (dd, 1H, J = 8.9, 2.4 Hz), 6.98 (s, 1H), 6.60 (d, 1H, J = 12.2 Hz), 4.02 (s, 3H), 3.99 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 161.8, 149.8, 149.0, 139.1, 139.0, 134.5, 132.1, 131.8, 131.6, 127.5, 114.9, 113.5, 113.4, 113.3, 56.2, 56.1, 55.5; HRMS (EI) calcd for $C_{18}H_{16}O_4$ [M^+] 296.1049, found 296.1045.

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Supporting Information Available: Detailed experimental procedures, characterization data, and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) On the basis of the observed pH values, we reasoned that the increased basic strength of the "old" *p*-TsONa (pH 10.38) would more facilitate the aldol condensation compared with the "new" one (pH 9.00). For ^{1}H NMR comparison, see the Supporting Information.