ORGANIC LETTERS

2009
Vol. 11, No. 3
555−558

Palladium-Catalyzed Sequential Arylation and Allylic Alkylation of Highly Functionalized Ketones: A Concise Synthesis of Mesembrine

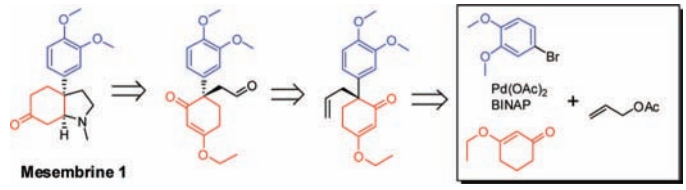
Yuanhong Zhao, Yongyun Zhou, Leilei Liang, Xiaodong Yang, Fengxiang Du, Liang Li, and Hongbin Zhang*

Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming, Yunnan 650091, P. R. China

zhanghb@ynu.edu.cn; zhang_hongbin@hotmail.com

Received November 12, 2008

ABSTRACT



An unprecedented palladium-catalyzed sequential procedure toward arylation and allylic alkylation of highly functionalized cyclohexenones was developed. This new protocol leads to useful building blocks containing a benzylic quaternary carbon in only one step. A concise total synthesis of mesembrine based on this procedure was achieved in only five steps with 22% overall yield.

Benzylic quaternary carbon centers are widely presented in bioactive natural products[1] (Figure 1). Efficient methodologies leading to the construction of such a quaternary carbon center represents one of the most synthetic challenge as well as powerful entry into the structurally diverse family of natural alkaloids.[2] Although synthetic efforts toward those units have generated a number of strategies or tactics over the years, many unfortunately fail to meet adequate measures of flexibility in terms of diversity-oriented synthesis.

Carefully analysis of the alkaloids shown in Figure 1, a common motif is characteristic and might be derived from synthetically valuable building blocks as shown in Scheme 1.

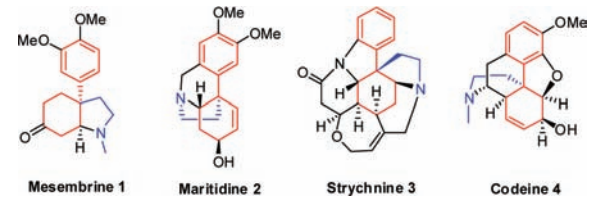


Figure 1. Important bioactive alkaloids and common unit presented in those structures.

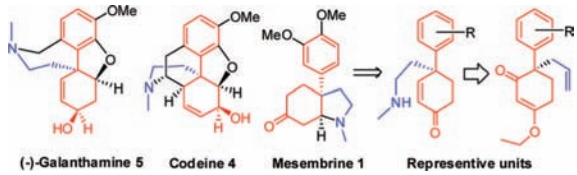
We envisaged that an arylation reaction followed by an allyl alkylation of a highly functionalized ketone, namely 3-ethoxy-

(1) For recent reviews, see: (a) Kornienko, A.; Evidente, A. *Chem. Rev.* **2008**, *108*, 1982–2014. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73–103. (c) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 111–126. (d) Zezula, J.; Hudlicky, T. *Synlett* **2005**, 388–405. (e) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278–311.

(2) For recent reviews, see: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396. (b) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473–1482. (c) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11934–11948. Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367. Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146.

10.1021/ol802608r CCC: $40.75
Published on Web 12/31/2008

Scheme 1. Retrosynthetic Analysis of Representative Alkaloids

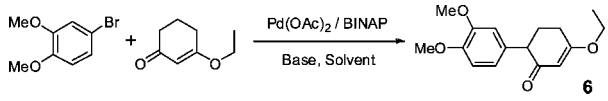


2-cyclohexenone, would provide the versatile building blocks for the synthesis of alkaloids as indicated in Figure 1.

Although palladium-mediated arylation of ketones has been well documented in the literature, mainly simple ketones being utilized as substrates.[3] Few attempts[4] have been made toward ketones in high functionality that is of importance for further synthetic manipulation. In this paper, we wish to report the preliminary results concerning construction of the benzylic quaternary carbon centers with a single-pot catalysis of different transformation strategy[5] and a concise route toward the total synthesis of (±)-mesembrine based on our new protocol.

With palladium acetate being a palladium source and racemic BINAP as a ligand, we initiated our studies on the arylation of 3-ethoxy-2-cyclohexenone, a commercially available starting material with rich functionality for further transformation. Our first arylation with 4-bromoveratrole in the presence of cesium carbonate in toluene ended in failure. After a few unsuccessful attempts, the desired arylation occurred when sodium bis(trimethylsilyl)amide being employed as a base in 1,4-dioxane at 90 °C (see Table 1).

Table 1. Arylation of Highly Functionalized Cyclohexanone[a]

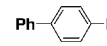
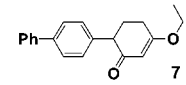
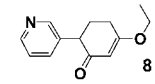
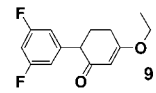
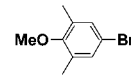
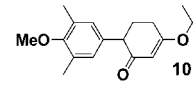
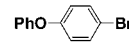
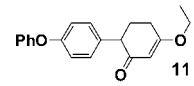
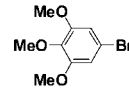
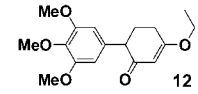
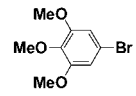
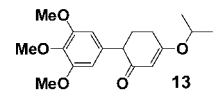


entry	time (h)	base	solvent	yield[b] (%)
1	24	Cs_2CO_3	toluene	0
2	24	^{t}BuOK	toluene	trace
3	24	$NaN(SiMe_3)_2$	toluene	<10
4	24	^{t}BuOK	1,4-dioxane	<10
5	24	$NaN(SiMe_3)_2$	1,4-dioxane	67
6	48	$NaN(SiMe_3)_2$	1,4-dioxane	70

[a] Reaction conditions: anhydrous 1,4-dioxane was freshly distilled from sodium benzophenone ketyl prior to use. Reactions in 1,4-dioxane were carried out in a 90 °C oil bath for 24−48 h. Reactions in toluene were carried out in a 100 °C oil bath. [b] Yields represent the isolated yield based on 3-ethoxy-2-cyclohexenone (average of two runs).

In order to get further insight toward the generality of this process, a number of aryl bromides were evaluated under optimized condition, mild to good yields were obtained. The results are summarized in Table 2. Although electron-neutral and electron-deficient aryl bromides could be used in this arylation, relatively low yields were obtained in both cases (entries 1 and 3 in Table 2).

Table 2. Palladium-Mediated Arylation under Optimized Conditions[a]

entry	ArBr	time	product	yield[b]
1		18 h	 7	35%
2		16 h	 8	25%
3		16 h	 9	14%
4		16 h	 10	69%
5		20 h	 11	56%
6		18 h	 12	72%
7		20 h	 13	64%[c]

[a] For reaction conditions, see the experimental section of stage 1. [b] Yields represent isolated yield based on 3-ethoxy-2-cyclohexenone. [c] 3-Isopropoxy-2-cyclohexenone was used instead of 3-ethoxy-2-cyclohexenone.

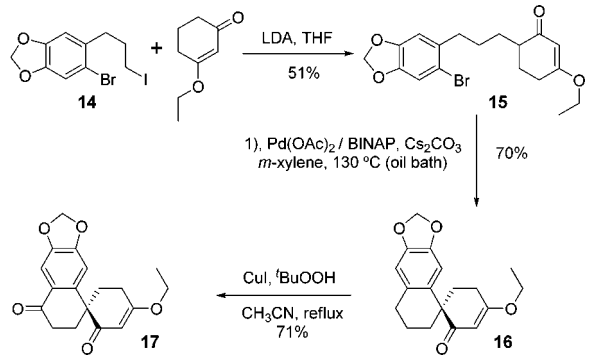
Aiming to extend this process toward the synthesis of structurally more complicated molecules, an intramolecular version for arylation of derivative of 3-ethoxy-2-cyclohexenone was then developed (see Scheme 2). Treatment of iodide **14** with 3-ethoxy-2-cyclohexenone in the presence of lithium diisopropylamide[6] afforded compound **15**. The intramolecular arylation was conducted in xylene in the presence of cesium carbonate, spirocyclic compound **16** being obtained in 70% yield. After oxidation with ^{t}BuOOH in the presence of cuprous iodide,[7] an interesting building

(3) (a) Liao, X.; Wang, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195–200. (b) Martin, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236–7239. (c) Ackermann, L.; Spatz, J. H.; Gschrei, C. J.; Born, R.; Althammer, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7627–7630. (d) Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413–1415. (e) Churruca, F.; SanMartin, R.; Carril, M.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2004**, *60*, 2393–2408. (f) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4526–4528. (g) Churruca, F.; SanMartin, R.; Tellitu, I.; Domi´nguez, E. *Tetrahedron Lett.* **2003**, *44*, 5925–5929. (h) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245. (i) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053–4056. (j) Sole, D.; Vallverdu, L.; Peidro, E.; Bonjoch, J. *Chem. Commun.* **2001**, 1888–1889. (k) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2001**, *57*, 5967–5974. (l) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370, and references cited therein.

(4) (a) Iwama, T.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 5725–5728. (b) Chae, J.; Yun, J.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 4809. (c) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261.

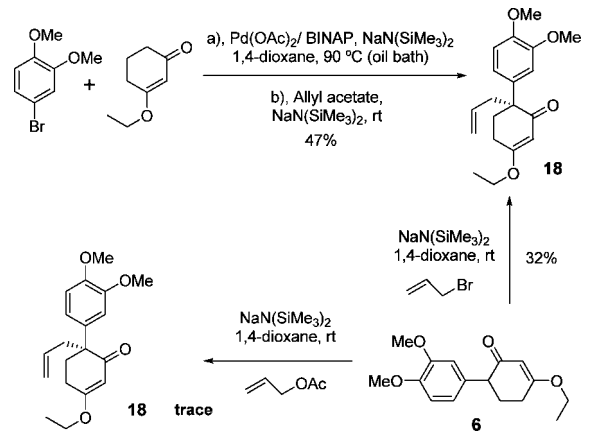
block, compound **17**, was obtained and should be of value toward the synthesis of natural products (Scheme 2).

Scheme 2. Intramolecular Palladium-Catalyzed Arylation of Enolates



Having established the arylation condition, our attention was then focused on the sequential palladium-mediated arylation−allylation, a "two birds with one metallic stone" protocol[4] which, we believed, would provide an efficient access to the quaternary carbon center in a single-pot catalysis. After the arylation, the reaction mixture was then cooled to room temperature and 2 equiv of sodium bis(trimethylsilyl)amide was added followed by addition of allyl acetate (2 equiv). To our delight, the desired product was isolated in 47% yield (Scheme 3). At that stage, it was

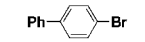
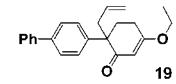
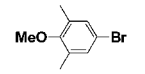
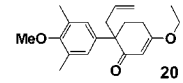
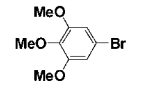
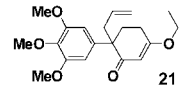
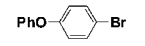
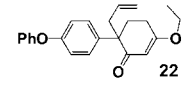
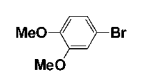
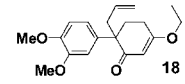
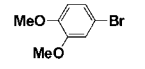
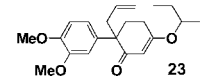
Scheme 3. Sequential Palladium-Catalyzed Arylation and Allylic Alkylation of Enolates



uncertain whether palladium participated in the allylation reaction or not. Control experiments with pure isolated α-arylketone **6** were then carried out. One reaction was conducted by treatment of ketone **6** with sodium bis(trimethylsilyl)amide and allyl acetate, another being carried out by treatment of ketone **6** with sodium bis(trimethylsilyl)amide and allyl bromide, both reaction being conducted in the absence of palladium and BINAP in anhydrous 1,4-dioxane at room temperature for 12 h. For reaction with allyl acetate, only trace alkylation was observed by thin-layer chromatography analysis. While in reaction with allyl bromide, compound **18** was obtained in 32% yield. Therefore, a Tsuji−Trost reaction rather than a simple allylation led to the desired product. To the best of our knowledge, this is the first example of palladium mediated sequential arylation−allylation reaction.

A number of sequential arylation−allylation reactions were conducted and the results are listed in Table 3. No substantial

Table 3. Palladium-Mediated Sequential Arylation−Allylation[a]

entry	ArBr	Pd source	product	yield[b]
1		$Pd(OAc)_2$		38%
2		$Pd(OAc)_2$		42%
3		$Pd(OAc)_2$		41%
4		$Pd(OAc)_2$		50%
5		$Pd_2(dba)_3$		47%[c]
6		$Pd(OAc)_2$		46%[d]

[a] For reaction conditions, see the Experimental Section. [b] Yields represent isolated yield based on aryl halides. [c] The reaction was carried out with R-BINAP. [d] 3-*sec*-Butoxy-2-cyclohexenone was used instead of 3-ethoxy-2-cyclohexenone.

difference was observed by variation of palladium sources. $Pd(OAc)_2$, $Pd_2(dba)_3$, and allylpalladium chloride dimer worked equally well in this sequential reaction. We also conducted the sequential reaction with *R*-BINAP, unfortunately, only 12% ee was obtained by chiral HPLC analysis on a Chiralcel OD-RH column.

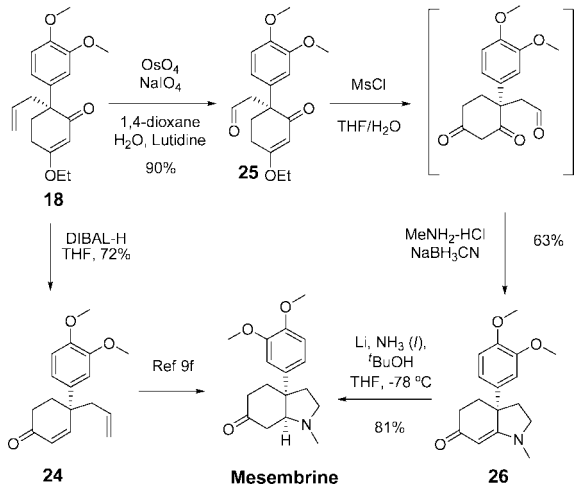
(5) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754–3760.

(6) Regiospecific allylation of 3-alkoxy-2-cyclohexenone was first introduced by Stork and Danheiser, see: Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775–1776.

(7) Salvador, J. A. R.; Sá eMelo, M. L.; Neves, A. S. C. *Tetrahedron Lett.* **1997**, *38*, 119–122.

(8) For bioactivities, isolation and structural determination of (−)-mesembrine, see: (a) Gericke, N. P.; Van Wyk, B. E. PCT Int. Appl. WO9746234, 1997; CAN 128: 80030. (b) Jeffs, P. W.; Hawks, R. L.; Farrier, D. S. *J. Am. Chem. Soc.* **1969**, *91*, 3831–3839. (c) Popelak, A.; Haack, E.; Lettenbauer, G.; Springler, H. *Naturwissenschaften* **1960**, *47*, 159.

Scheme 4. Total Synthesis of (±)-Mesembrine



In order to demonstrate the importance of these allylated ketones, vinylogous ketone **18** was converted to the serotonin uptake inhibitor mesembrine 1.[8] Diisobutylaluminum hydride (DIBAL-H) reduction of **18** afforded **24**, a known mesembrine precursor.[9] Alternatively, oxidative cleavage of the allyl group of compound **18**[10] gave the aldehyde **25**. Hydrolysis of **25** afforded the crude aldehyde dione, which on reductive amination[11] was converted to the vinylogous amide **26** in 63% yield over two steps. Birch reduction converted **26** to (±)-mesembrine **1**[12] in five steps and 22% overall yield from commercial materials.

In summary, we have developed an unprecedent sequential procedure for palladium catalyzed arylation and allylic alkylation of highly functional ketones. This new protocol leads to useful building blocks in only one step. The highly functional cyclohexenone derivatives represent one of the most valuable synthons for the synthesis of natural products that containing a benzylic quaternary carbon center. On the basis of the new protocol, a concise total synthesis of mesembrine was achieved in only five steps with 22% overall yield.

Acknowledgment. This work was supported by a grant (20662011) from the National Natural Science Foundation of China and partially supported by a grant from the foundation of the Chinese Ministry of Education for fostering important scientific research programs (706052). We thank the Yunnan Provincial Science & Technology Department for financial support (2007B0006Z).

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, MS, as well as HRMS spectra of all key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802608R

(9) For recent synthesis of mesembrine, see: (a) Roe, C.; Sandoe, E. J.; Stephenson, G. R.; Anson, C. E. *Tetrahedron Lett.* **2008**, *49*, 650–653. (b) Tam, N. T.; Cho, C.-G. *Org. Lett.* **2007**, *9*, 3391–3392. (c) Arns, S.; Lebrun, M.-E.; Grisé, C. M.; Denissova, I.; Barriault, L. *J. Org. Chem.* **2007**, *72*, 9314–9322. (d) Paul, T.; Malachowski, W. P.; Lee, J. *J. Org. Chem.* **2007**, *72*, 930–937. (e) Paul, T.; Malachowski, W. P.; Lee, J. *Org. Lett.* **2006**, *8*, 4007–4010. (f) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711–7714. (g) Chavan, S. P.; Khobragade, D. A.; Pathak, A. B.; Kalkote, U. R. *Tetrahedron Lett.* **2004**, *45*, 5263–5265. (h) Song, Z. L.; Wang, B. M.; Tu, Y. Q.; Fan, C. A.; zhang, S. Y. *Org. Lett.* **2003**, *5*, 2319–2321. (i) Kulkarni, M. G.; Rasne, R. M.; Davawala, S. I.; Doke, A. K. *Tetrahedron Lett.* **2002**, *43*, 2297–2298. (j) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143–147, and references cited therein.

(10) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.

(11) (a) Hoshino, O.; Sawaki, S.; Shimamura, N.; Onodera, A.; Umezawa, B. *Chem. Pharm. Bull.* **1987**, *35*, 2734–2743. (b) Hoshino, O.; Sawaki, S.; Shimamura, N.; Onodera, A.; Umezawa, B. *Heterocycles* **1978**, *10*, 61–66.

(12) Takano, S.; Imamara, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479–4482.