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Benzazepine Ring Formation *via* an Intramolecular Heck Reaction: Synthetic Application to Chilenine

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Benzazepine alkaloids such as chilenine **1** and cephalotaxine **2** have been attractive synthetic targets by many synthetic research groups mainly because of their skeletal challenge (Figure 1).[1] Numerous attractive ways have been developed and most of the synthetic approaches to the skeleton have been focused on the cyclization forming the central 7-membered azepine ring.[2] There have been several reports of azepine formation through Heck-type reactions, however, only a few synthetic applications to natural alkaloids from the intermediates obtained has been reported.[3]

As an extension of our development of natural azepine alkaloids,[4] we wanted to explore an intramolecular Heck reaction with precursor **3** for the formation of 7-membered ring and the transformation to chilenine thereafter. And we expected to apply oxidative conditions for the formation of the 5-membered ring of chilenine from **4** (Scheme 1).

In this communication, we wished to suggest a sequential bicyclization process from intermediate **4** in one pot. The precursor **5** would be prepared concisely from **4** which would be prepared concisely from the known compounds (Scheme 1).[5,6]

For the preliminary investigation of the desired cyclization, we prepared bromide precursor **5** to make a model compound **6**.[5] From several trials, an applicable condition could be

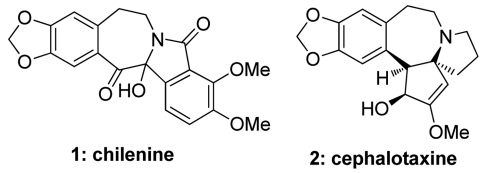
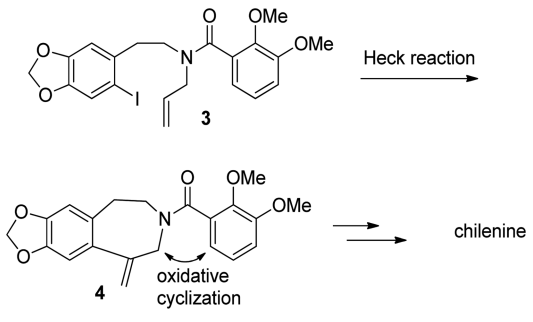
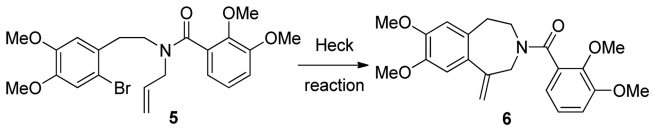


Figure 1



Scheme 1

Table 1. Heck reaction conditions for the cyclization of **5**



Entry	Palladium (equiv)	Conditions (140 °C in sealed tube)	Yield[a] (%) of **6**
1	$Pd(dppf)Cl_2$ (0.1 equiv.)	DBU (2 equiv.), THF, 14 h	13%
2	$Pd(dppf)Cl_2$ (0.1 equiv.)	DIEA (2 equiv.), DMF, 10 h	14%
3	$Pd(dppf)Cl_2$ (0.1 equiv.)	DBU (2 equiv.), DMF, 16 h	42%
4	$Pd(dppf)Cl_2$ (0.1 equiv.)	Et_3N (2 equiv.), THF, 16 h	72%
5	$Pd(PPh_3)_4$ (0.1 equiv.)	DBU (2 equiv.), THF, 12 h	11%

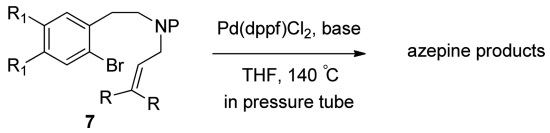
[a]Isolated yield.

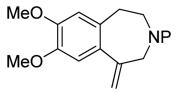
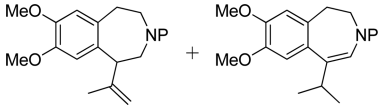
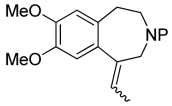
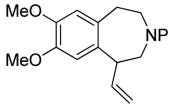
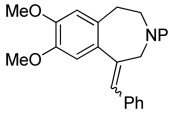
selected (entry 4) ($Pd(pddf)Cl_2$, Et_3N, THF in pressure tube at 140 °C) (Table 1).

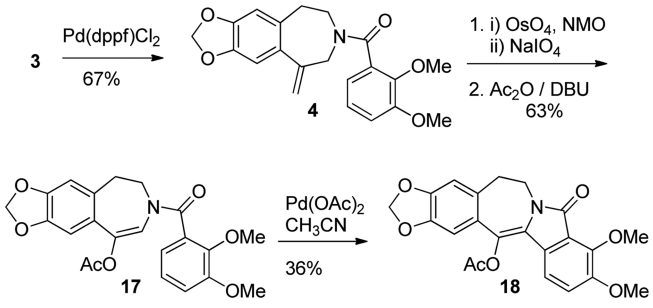
The scope and the limit of this reaction have been searched (Table 2). The condition using Hunig's base instead of Et_3N afforded better results for the related derivatives. Depending on allylic moieties on amide, the ratio of double bond in *exo* or *endo* position of the product has varied (entry 3, 6, 7) and the yields were ranged from moderate to good (15% to 76%).

Synthetic application to chilenine was readily tried the requisite molecule **3**.[6] The Heck reaction condition selected in Table 1 yielded azepine **4** in 67% yield. The next cyclization of **5** or the benzoyl azepin-5-one intermediate formed by oxidative cleavage of the exo-methylene group has failed, so the desired oxidative cyclization was performed from the enol lactone **17** to afford **18**, a known precursor for chilenine.[7] Compound **17** was prepared by dihydroxylation with OsO_4 followed by oxidative cleavage to ketone, and *O*-acylation of the ketone with Ac_2O under heating at 90 °C in DMF in the presence of excess DBU (64% yield for the three step sequence).[8] Compound **17** was found to be tenacious against cyclization as well as oxidation, only forcing condition (2-3 equiv. $Pa(OAc)_2$ with or without co-oxidant benzoquinone in refluxing CH_3CN overnight) enabled the conversion to allow 30 to 36% yields of **18**.[9] The final transformation of **18** to chilenine has been repeated by the known procedure, dihydroxylation using OsO_4 followed by H_2S treatment, suggesting a new way to a concise formal

Table 2. Cyclization study of **7**



Entry		Product
1	P: Boc	 **8**: 40%
2	P: Boc	 **9**: 34% **10**: 45%
3	P: Bz	**11**: 17% **12**: 55%
4	P: Boc	 **13**: 20% (single isomer)
5	P: Bz	 **14**: 15% (single isomer)
6	P: Boc	 **15**: 76% (single isomer)
7	P: Bz	**16**: 75% (single isomer)



Scheme 2

synthesis of chilenine.

In summary, a palladium-catalyzed cyclization reaction of aryl halides containing allylic moiety provided azepine skeletons, and the following manipulation including an oxidative cyclization allowed a concise route to chilenine.

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5. Bomination of 3,4-dimethoxyphenethylamine in acetic acid (85%), bezoylation with 2,3-dimethoxybenzoyl chloride (92%), and allylation with allyl bromide in the presence of NaH and Bu_4NBr (95%) provided **5**.
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7. Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 2747-2750.
8. Compound **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.14-7.10 (m, 2H), 7.00-7.97 (m, 2H), 6.84-6.80 (m, 3H), 6.70 (s, 1H), 6.68 (s, 1H), 6.52 (s, 1H), 6.47 (s, 1H), 5.96 (s, 2H), 5.94 (s, 2H), 4.19 (m, 2H), 3.90 (s, 3H), 3.84-3.76 (m, 7H), 3.57 (m, 1H), 3.08 (m, 2H), 2.99-2.96 (m, 2H), 2.29 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.2, 167.7, 166.9, 152.9, 152.8, 147.5, 147.4, 146.9, 146.8, 145.5, 145.2, 134.2, 133.7, 133.4, 132.0, 130.5, 130.3, 126.3, 125.1, 124.7, 121.6, 119.5, 119.2, 118.8, 113.9, 113.6, 109.5, 105.3, 105.1, 101.4, 61.7, 61.5, 55.9, 50.3, 48.2, 35.6, 34.1, 20.9.
9. Compound **18**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.54 (d, J = 8.5 Hz, 1H), 7.12 (d, J = 8.6 Hz, 1H), 6.91 (s, 1H), 6.68 (s, 1H), 5.98 (s, 2H), 4.07 (s, 3H), 3.93 (s, 3H), 3.91-3.96 (bm, 2H), 3.07 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.5, 163.6, 153.4, 148.1, 147.4, 147.3, 134.4, 130.3, 129.0, 127.6, 126.9, 121.3, 119.6, 116.6, 109.9, 105.6, 101.6, 62.5, 56.7, 43.3, 34.8, 21.4.