Communication

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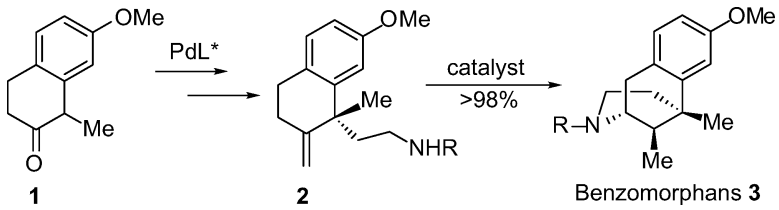

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Migratory Hydroamination: A Facile Enantioselective Synthesis of Benzomorphans

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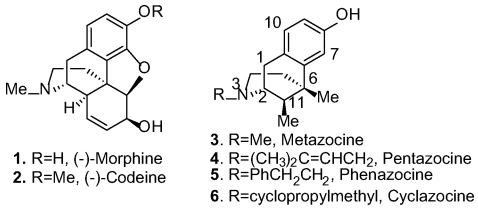
Naturally occurring (−)-morphine is extremely important as an analgesic but suffers from side effects such as addiction.[1] Much effort has been devoted to overcoming this problem by structural modification.[2] As a result, certain nonnatural benzomorphans and morphinans have succeeded in reducing the addicting effect to a considerable extent, such as the clinically used pentazocine **4** and phenazocine **5**.[3] In addition to their use as analgesics, benzomorphans are also useful in the treatment of cocaine addiction (e.g., **6**).[4] Not surprisingly, pharmacological activity in these series is dramatically dependent on absolute configuration. For example, (−)-pentazocine is 20 times more potent than its enantiomer.[5] Despite the importance of benzomorphans, previous enantioselective syntheses of benzomorphans (**3**−**6**, Figure 1) utilized either resolution[6] or chiral auxiliaries[7−9] all through Grewe-type cyclizations[2,10] with one exception.[11]



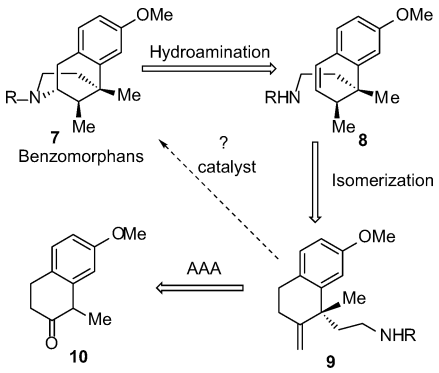
1. R=H, (-)-Morphine
2. R=Me, (-)-Codeine
3. R=Me, Metazocine
4. R=$(CH_3)_2C{=}CHCH_2$, Pentazocine
5. R=$PhCH_2CH_2$, Phenazocine
6. R=cyclopropylmethyl, Cyclazocine

Figure 1. Opium alkaloids and benzomorphans.

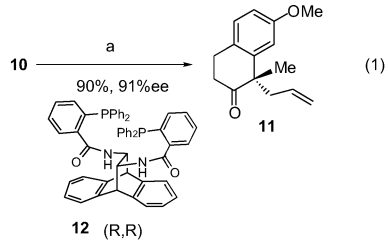
We[12] recently described a new asymmetric synthesis of opium alkaloids (**1** and **2**) involving a novel base-promoted intramolecular hydroamination[13] which requires tungsten light irradiation. This reaction forges the key piperidine ring of this family of alkaloids, which previously were cyclized using stoichiometric mercury salts[14] or via the chromium tricarbonyl complex[15] from free amine. The benzomorphans served as an ideal target to gain better understanding of the key cyclization reaction and assess the possibility of establishing the rather challenging benzylic quaternary carbon center[16] through palladium-catalyzed asymmetric allylic alkylation (AAA) of a prochiral ketone.[17] In formulating a route (Scheme 1), we envisioned two olefinic intermediates **9** and **8**, the former to set the stereochemistry of the methyl group and the latter to effect cyclization. Typically, the conversion of **9** to **8** involves multiple steps requiring stoichiometric reduction and oxidation. Inspired by a recent report of intermolecular hydroamination of allyl- and homoallylbenzene,[18] the fact that benzomorphan **7** itself is an isomer of olefin **9** emboldened us to ask a conceptually intriguing question. *Is it possible to cycloisomerize **9** to **7** diastereoselectively in one catalytic step by a migratory hydroamination?* In this communication we explore the cycloisomerization via a catalytic migratory hydroamination and the power of palladium-catalyzed AAA of a prochiral ketone for simplifying problems in alkaloid synthesis.

Discrimination of enantiotopic faces of the nucleophile in the palladium-catalyzed AAA is very challenging as the nucleophile attacks on the face of the π-allyl system opposite to that of the

Scheme 1. Retrosynthetic Analysis



chirality inducing metal−ligand complex.[19] Gratifyingly, performing the allylic alkylation of tetralone **10**[20] and allyl acetate with a catalyst derived from π-allylpalladium chloride dimer (0.5%) and (*R*,*R*)-ligand **12** (1.0%) in the presence of cesium carbonate[21] in DME gave **11** in good yield and ee as shown in eq 1.



(1)

a) allylacetate (1.1eq.), 0.5% $(\eta^3\text{-}C_3H_5PdCl)_2$, 1.0% **12**, DME, Cs_2CO_3, -15^{0}C.

Wittig olefination gave almost quantitative yield of exocyclic olefin **13** (Scheme 2). Although one-pot cleavage (OsO_4, $NaIO_4$) of **13** was not successful, stepwise operations selectively cleaved the less hindered terminal olefin in the presence of the 1,1-disubstituted olefin. Reductive amination provided amine **15** in good yield.

The stage was set for the key speculative step, the migratory hydroamination. Treatment of amine **15** with a catalytic amount or even a full equivalent of LDA gave only recovered starting material, presumably due to the difficulty of the initial isomerization. Thus, we examined the isomerization under acidic conditions and found the exocyclic olefin was isomerized to the internal olefin **16** (not all the way to conjugation!). Despite the need to isomerize **16** to **8** (R = CH_3) first and the difficulty of subsequent addition of a lithium amide to an electron-rich styrene,[12,22] subjecting amine **16** to 20 mol % LDA in THF led to cycloisomerization to form **17** as a single diastereomer[23] in less than 30 min at room temperature. This result suggests that the failure of cyclization using base alone in the case of morphine might be due to the more electronically rich aromatic ring compared to benzomorphans. Increasing the basicity

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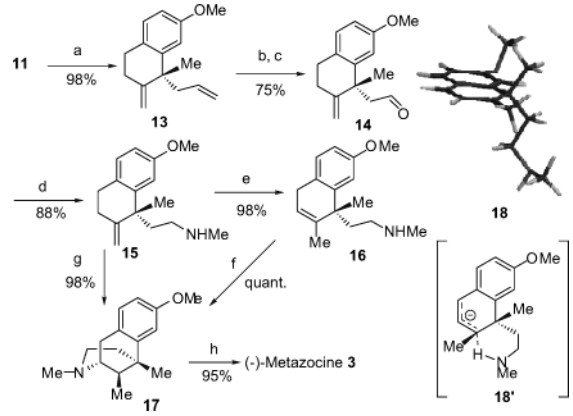
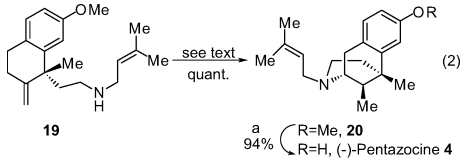
Scheme 2. Synthesis of (−)-Metazocine[a]



[a] Reaction conditions: a) CH_2═PPh_3, THF; b) 2% OsO_4, NMO; c) $NaIO_4$; d) $MeNH_2$, $MgSO_4$, $NaBH_4$; e) 1.5 equiv TsOH, toluene, reflux; f) 20 mol % BuLi, 20 mol % *i*Pr_2NH, THF, rt, 30 min; g) 20 mol % BuLi, 20 mol % *i*Pr_2NH, 40 mol % TMEDA, THF, rt, 8 h; h) BBr_3, CH_2Cl_2.

of the medium by addition of 40 mol % TMEDA[18] allowed reaction of **15** and provided **17** more slowly (8 h) but still nearly quantitatively. We hypothesized that the high diastereoselective control of C-11 came from intramolecular protonation of the allylic anion **18** from the alpha face (i.e., cis to the aminoethyl substituent as depicted in **18′**) of an almost flat six-membered ring. This is in contrast to previous approaches employing Grewe cyclizations which often gave both epimers.[7,24] Finally, demethylation gave (−)-metazocine (**3**), whose spectral data is identical to that previously reported.[7,9]

To test the scope and selectivity of the migratory hydroamination, amine **19** was prepared from **14** in a similar way (85% yield) and treated with the catalyst system as for **15** (eq 2). Amine **20** was obtained in quantitative yield as a single diastereomer. It is noteworthy that the olefin of the prenyl substituent was unchanged. Demethylation with NaSEt provided (−)-pentazocine (**4**)[25] cleanly. Thus, simply changing the amine in the reductive amination allows easy variation of the N substituent.



a) NaSEt, DMF, 130°C, 5h.

In conclusion, we have developed a highly efficient general strategy for the enantioselective synthesis of benzomorphans (46% and 45% overall yield from commercially available material for (−)-metazocine and (−)-pentazocine, respectively). It demonstrates for the first time the efficacy of palladium-catalyzed AAA of simple ketones in the context of complex synthesis. The unprecedented diastereoselective migratory hydroamination addresses the control of C-11 stereogenic center, and should have many applications in alkaloid synthesis. The strategy outlined here opens the way to access either enantiomer[26] of a variety of C-6, C-11, and N-3 substituted benzomorphan analogues.

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Supporting Information Available: Experimental details and analytical data for all new compounds and data for synthetic benzomorphans (PDF). This material is available free for charge via the Internet at http://pubs.acs.org.

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