Synthetic study of (−)-morphine using organocatalyst

(*Graduate School of Science, Tohoku University*) ○ Yutaro Hatano, Naoki Mori, Yujiro Hayashi

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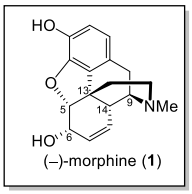
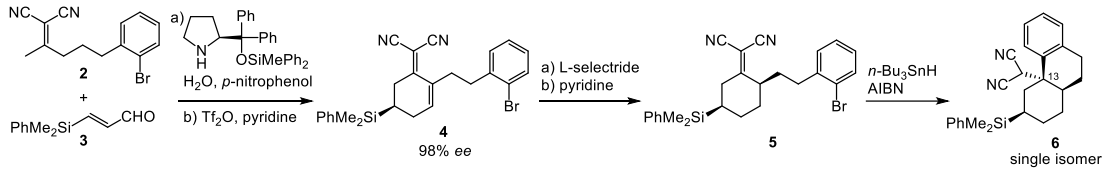
(−)-Morphine (**1**) is an important alkaloid which has a strong analgesic activity. Since previous total syntheses of morphine have required many steps due to its complex structure including a quaternary center at C13, a more efficient total synthesis is desired for the further medicinal studies.

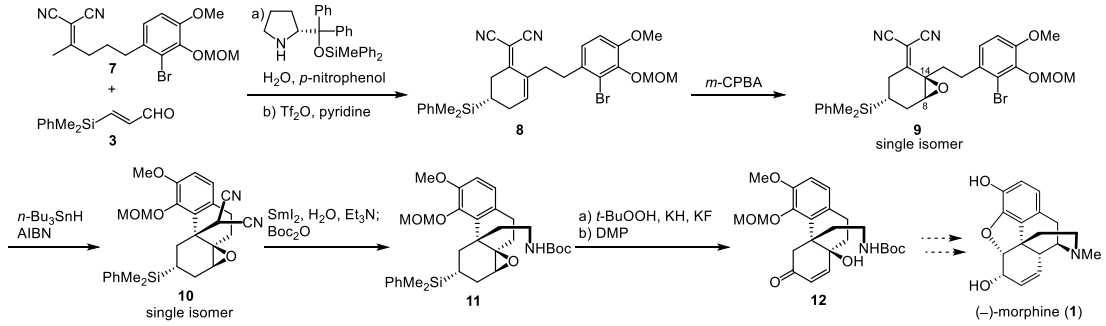


Firstly, we studied a construction of a quaternary center using a model substrate **2** (Scheme 1). Recently, we developed asymmetric [3+3] cycloaddition of alkylidene malononitrile and α,β-unsaturated aldehyde using diphenylprolinol silyl ether.[1] Asymmetric [3+3] cycloaddition of **2** and **3**, followed by dehydration afforded **4** with excellent enantioselectivity. 1,6-Reduction followed by epimerization gave **5**. After several screenings of the reaction conditions to construct a quaternary center at C13, we found that intramolecular radical cyclization worked efficiently to afford a desired product **6** as a single isomer.



Scheme 1. Model study to access an asymmetric quaternary center

Since we succeeded in construction of the carbon skeleton of **1**, we moved to a synthetic study using **7** (Scheme 2). Asymmetric [3+3] cycloaddition of **7** and **3** followed by dehydration afforded **8**. Regioselective and stereoselective epoxidation with *m*-CPBA afforded epoxide **9**. Intramolecular radical cyclization of **9** gave **10** as a single isomer. Reductive decyanation, amine formation and Boc protection afforded **11** in one-pot. Tamao-Fleming oxidation and DMP oxidation gave **12**. The further transformation to synthesize **1** is in progress.



Scheme 2. Synthetic study of morphine

1) Y. Hayashi *et al.*, *Eur. J. Org. Chem.* **2022**, e202200603.