Catalytic Asymmetric Total Syntheses of (–)-Morphine and (–)-Codeine

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(–)-Morphine (**1a**, Figure 1) is one of the most important and efficient analgesic drugs in the clinic and has been continuously ranked among the World Health Organization (WHO) model lists of essential medicines since 1977. Architecturally, (–)-morphine possesses a synthetically challenging pentacyclic framework containing five contiguous stereocenters. Therefore, (–)-morphine and several related alkaloids have attracted a considerable amount of research interest from the synthetic and pharmaceutical communities, and more than 30 total or formal synthetic routes have been reported. However, the catalytic and enantioselective total synthesis of (–)-morphine has not been extensively explored yet and the asymmetric construction of the crucial all-carbon quaternary stereocenter remains a major challenge. Professor Yong-Qiang Tu from Lanzhou University (P. R. of China) explained: "The existing catalytic asymmetric syntheses of (–)-morphine exhibit common drawbacks, including: (1) long synthetic routes, (2) low overall yields and unsatisfactory enantioselectivity, and (3) the lack of direct and catalytic asymmetric construction of the key chiral quaternary carbon or AEC ring system

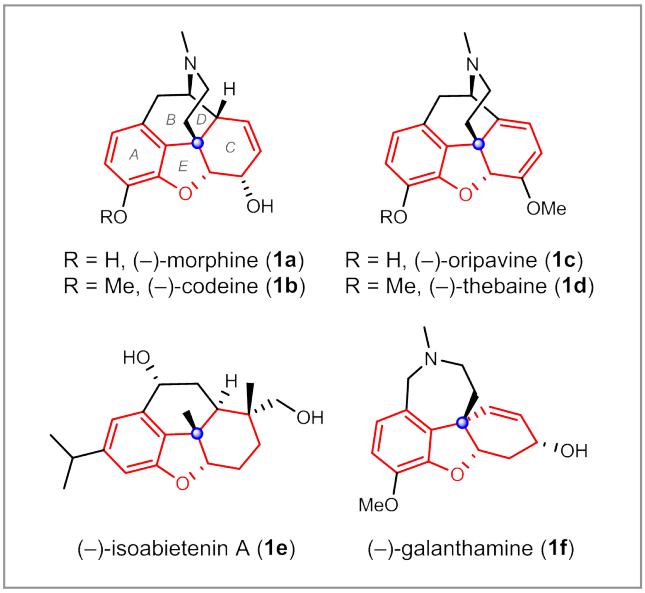


Figure 1 Morphine and several structurally related natural products

from racemic starting materials. Thus, we felt that a concise and efficient catalytic enantioselective total synthesis of (–)-morphine was much needed."

Recently, Professor Tu and Professor Fu-Min Zhang, also at Lanzhou University, reported the catalytic asymmetric total syntheses of (–)-morphine and (–)-codeine *via* a highly enantioselective Robinson annulation. "Since 2010 our group has focused on the design and preparation of novel chiral ligands or catalysts based on spirocyclic pyrrolidine (SPD) and spirocyclic amide (SPA) backbones. And these catalysts have successfully facilitated several asymmetric reactions (*Chem. Commun.* **2015**, *51*, 9979–9982; *Org. Lett.* **2017**, *19*, 6618–6621; *J. Am. Chem. Soc.* **2018**, *140*, 10099–10103)," said Professor Tu. He continued: "As a continuation of this research subject for further expanding the application of our SPD catalysts, the asymmetric total synthesis of (–)-morphine was undertaken."

The designed enantioselective Robinson annulation reaction was initially investigated by the graduate student Qing Zhang, who found that some commonly used secondary amine catalysts could not catalyze this reaction. However, the intramolecular Michael adduct **3** could be isolated (Scheme 1). "The asymmetric synthesis of such functionalized hydrobenzofuran bearing a quaternary carbon center has rarely been reported, and, importantly, the enantioselectivity of the Michael addition is vital for obtaining the enantioenriched tricyclic product **4**. Therefore, an extensive investigation of this asymmetric Michael reaction was carried out," Professor Tu explained.

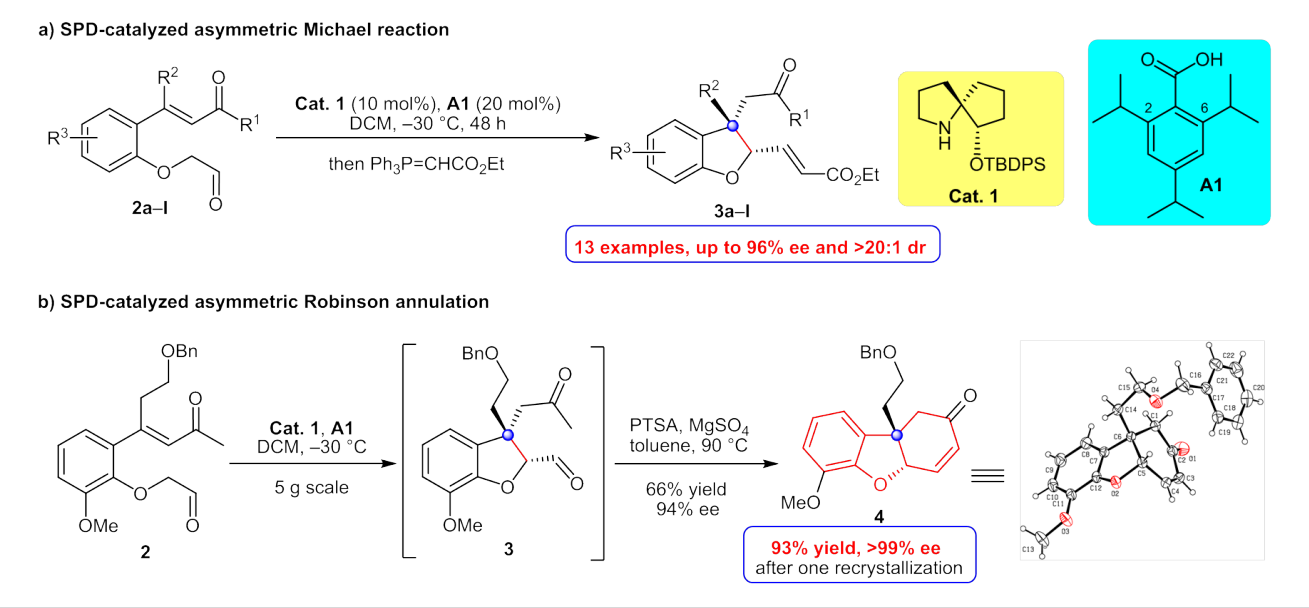
Under the guidance of Professor Fu-Min Zhang, Qing Zhang screened a number of catalysts and additives. "We found that the steric hindrance of the substituents at C2 and C6 positions of benzoic acid derivatives had a significant capacity to improve the enantioselectivity of the Michael addition. Among them, the more sterically bulky additive 2,4,6-triisopropylbenzoic acid (**A1**) in the presence of our developed SPD catalyst (**Cat.1**) gave the best result (96% ee)," commented Professor Zhang. He added: "As a matter of fact, in asymmetric aminocatalysis it is extremely rare to observe such an intriguing substituent effect in an additive." Subsequently, a series of structurally varied substrates were explored in the SPD-catalyzed Michael addition. Excellent enantio- and diastereoselectivities (up to 96% ee and >20:1 dr) as well as good to high yields (up

to 87% yield) were obtained (Scheme 1, a). "This work represents an important advance in utilizing the SPD catalysts. It also demonstrates that our developed SPD catalysts possess unique catalytic properties for the asymmetric construction of the synthetically challenging all-carbon quaternary stereocenter," Professor Tu remarked.

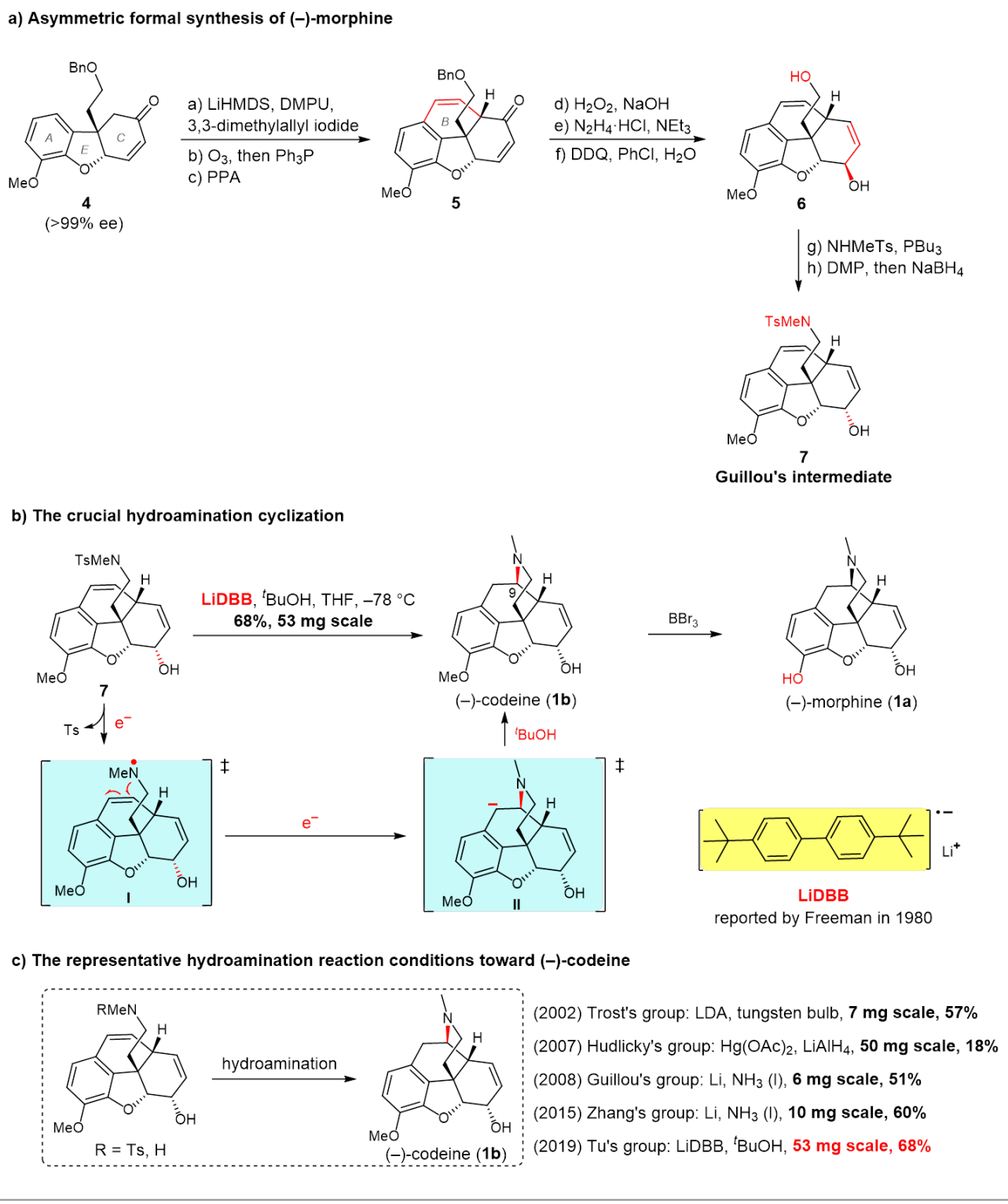
After developing the SPD-catalyzed intramolecular Michael reaction, Qing Zhang successfully achieved the one-pot enantioselective Robinson annulation and further increased the enantiopurity (>99%) of the tricycle product **4** by recrystallization (Scheme 1, b). Professor Tu explained: "This key Robinson annulation reaction can efficiently construct the highly functionalized *cis*-hydrodibenzofuran framework bearing two contiguous stereocenters, including an all-carbon quaternary center, in a one-pot chemical manipulation." He continued: "Notably, the current asymmetric transformation may be applied in the syntheses of a series of structurally related bioactive natural products, such as abietane diterpene (–)-isoabietenin A (**1e**) or clinical drugs, such as (–)-galanthamine (**1f**) (Figure 1)."

Having efficiently assembled the AEC ring system of (–)-morphine, the authors turned their attention on accomplishing the total synthesis of the target molecule **1a** (Scheme 2, a). "After screening a number of reaction conditions, we successfully constructed the B ring of (–)-morphine by Friedel–Crafts reaction over three steps. Subsequently, the transformation of tetracyclic enone **5** to allylic alcohol **6** was achieved by a Wharton reaction. Finally, a highly regioselective Mitsunobu reaction of compound **6**, followed by the inversion of configuration of the allylic alcohol, produced Guillou's intermediate **7**," remarked Professor Tu. He added: "Actually, at this point, we had completed the asymmetric formal synthesis of (–)-morphine."

In the final effort towards (–)-morphine, Professor Tu and his co-workers explored an alternative approach to the efficient construction of the C-9 stereocenter. "Mechanistically, this ring-forming reaction probably proceeds through a single-electron reduction of the sulfonamide unit to produce a nitrogen radical, which undergoes a subsequent radical addition/reduction/protonation sequence to generate (–)-codeine (**1b**) (Scheme 2, b). We speculated that after the formation of an active nitrogen radical, the next regio- and stereoselective intramolecular ring-closing procedure should readily occur in view of the annular strain and the conformational features of the morphine scaffold," Professor Tu explained. He continued: "Therefore, we considered that the mild and readily available free radical initiator, lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB) (*J. Org. Chem.* **2016**, *81*, 10707–10714) might be a suitable reagent to initiate this transformation. As we expected, the crucial hydroamination cyclization proceeded well, which efficiently provided the desired (–)-codeine (**1b**) in higher yield (68%)." Professor Tu remarked: "Notably, in comparison to the previously reported results (Scheme 2, c), this novel methodology exhibited a remarkable superiority



Scheme 1 SPD-catalyzed enantioselective Michael reaction and Robinson annulation

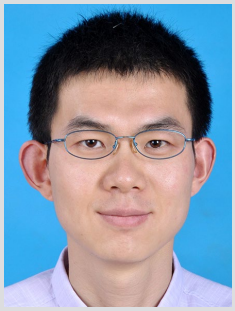


Scheme 2 The asymmetric total syntheses of (–)-codeine and (–)-morphine

in terms of higher chemical yield, larger synthetic scale, and better reproducibility." Finally, (–)-codeine (**1b**) was easily converted into (–)-morphine (**1a**) *via* demethylation with BBr_3 in high yield.

Professor Tu concluded: "In summary, the concise and catalytic asymmetric total syntheses of (–)-codeine and (–)-morphine were accomplished from commercially available but-3-yn-1-ol over 15 and 16 steps, respectively. The highly efficient SPD-catalyzed enantioselective Robinson annulation is not only able to construct the AEC tricyclic nucleus of the target molecules, but also showcases the excellent catalytic properties of our developed SPD catalysts. Additionally, the current study provides the first example of the synthesis of (–)-morphine through direct and catalytic asymmetric construction of the synthetically challenging all-carbon quaternary stereocenter. Finally, this asymmetric synthetic route constitutes an effective approach to the preparation of (–)-morphine and its analogues. Further synthetic applications of this methodology and significant exploration of the SPD-catalyzed tandem reaction are currently in progress in our labs."

About the authors



Q. Zhang

Qing Zhang is from Dezhou, Shandong Province, P. R. of China. He obtained his B.S. degree from Shandong Normal University (P. R. of China) in 2013. Then he joined Professor Yong-Qiang Tu's group at Lanzhou University (P. R. of China) as a PhD candidate. Now his research interests mainly focus on asymmetric catalysis and total syntheses of natural products.

Prof. F.-M. Zhang

Fu-Min Zhang received his MS (2001) and PhD (2006) degrees from Lanzhou University (P. R. of China) under the supervision of Professor Xuan Tian and Professor Yong-Qiang Tu, respectively. He worked as a postdoctoral fellow at the Mayo Clinic (USA) with Professor Yuan-Ping Pang (2007–2008). He returned to Lanzhou University as a lecturer and was then appointed as an associate professor in 2009 and a full professor in 2014. Currently, he is interested in the total syntheses of natural products and relative synthetic methodology.

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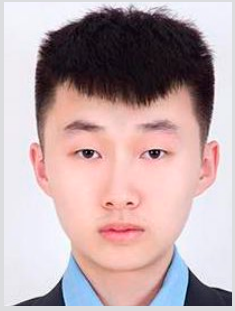
Chang-Sheng Zhang was born in Jiangxi Province, P. R. of China. He received his Bachelor's degree from Zhengzhou University (P. R. of China) in 2016. He then moved to Lanzhou University (P. R. of China) for his Master's degree under the supervision of Professor Yong-Qiang Tu. His research interests focus on developing new SPD-type ligands and applying them to new asymmetric reactions.



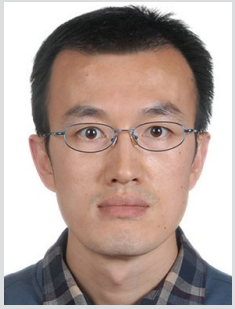
S.-Z. Liu

Si-Zhan Liu was born in Hebei Province, P. R. of China. He received his Bachelor's degree from Lanzhou University (P. R. of China) in 2018. Now he is studying for his Master's degree under the supervision of Professor Shao-Hua Wang at the School of Pharmacy, Lanzhou University. Currently, his research interests involve the development of novel synthetic methodologies.

Dr. J.-M. Tian

Jin-Miao Tian received his PhD from Lanzhou University (P. R. of China) in 2016 under the supervision of Professor Yong-Qiang Tu and then moved to Shanghai Jiao Tong University (P. R. of China) as a postdoctoral associate with Professor Yong-Qiang Tu. There his research focused on developing new SPD-type ligands and organocatalysts and applying them in asymme-

tric catalysis. Currently, he is a research associate at the Institute of Molecular Medicine (IMM), Renji Hospital, Shanghai Jiao Tong University School of Medicine. His research now focuses on aptamer-based biological applications.



Prof. S.-H. Wang

Shao-Hua Wang obtained his PhD in organic chemistry from Lanzhou University (P. R. of China) with Professor Yong-Qiang Tu in 2006. From 2006 to 2011, he was a postdoctoral associate in Professor Yuan-Ping Pang's group at the Mayo Clinic (USA). In 2011, he was appointed as an associate professor at the School of Pharmacy, Lanzhou University. His current research interests involve the development of synthetic methodologies and their application in the syntheses of natural products, and medicinal chemistry.

Dr. X.-M. Zhang

Xiao-Ming Zhang studied chemistry at Lanzhou University (P. R. of China) where he received his BS in 2007. He then joined the research group of Professor Yong-Qiang Tu and completed his PhD at Lanzhou University in 2013. Currently, he is a lecturer at the Department of Chemistry, Lanzhou University. His research mainly focuses on total syntheses and biomimetic syntheses of natural products.

Prof. Y.-Q. Tu

Yong-Qiang Tu received his BS and MS degrees from Lanzhou University (P. R. of China) in 1982 and 1985, respectively. He obtained his PhD in organic chemistry in 1989 from Lanzhou University under the supervision of Professor Yao-Zu Chen. After spending three years (1993–1995) as a postdoctoral fellow in W. Kitching's group at Queensland University, Australia, he was appointed to a full professor position at Lanzhou University in 1995 and became Director of the State Key Laboratory of Applied Organic Chemistry from 2001 to 2010. In 2009, he was elected as Academician of the Chinese Academy of Sciences. His current research interests mainly center on the development of novel chiral ligands or catalysts, and their application to new asymmetric reactions, as well as the total syntheses of bioactive natural products.