DMSO-Catalyzed Late-Stage Chlorination of (Hetero)arenes

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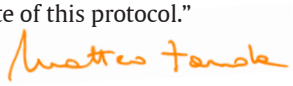
Chlorinated (hetero)arenes are widely used in organic synthesis and in pharmaceuticals. Professor Ning Jiao – an organic synthesis expert at Peking University (P. R. of China) – pointed out that Pfizer systematically screened more than 220,000 aryl derivatives and found that aromatic chlorination may change the physicochemical properties of drugs, such as pK_a, dipole moment, as well as metabolic rate, therefore improving pharmacokinetic and pharmacological properties (*Drug Metab. Lett.* **2011**, *5*, 232–242). "As the Nobel Laureate James Black stated, '*the most fruitful basis for the discovery of a new drug is to start with an old drug*' (*Lancet* **2000**, *355*, 1022), therefore, late-stage chlorination may provide a reliable shortcut for the discovery of new drugs," said Professor Jiao. Although some elegant chlorination reactions have been developed these protocols suffer from either the high cost of the chlorinating reagents or harsh conditions. "Therefore, the efficient and practical late-stage chlorination of bioactive molecules remains formidably challenging," he added.

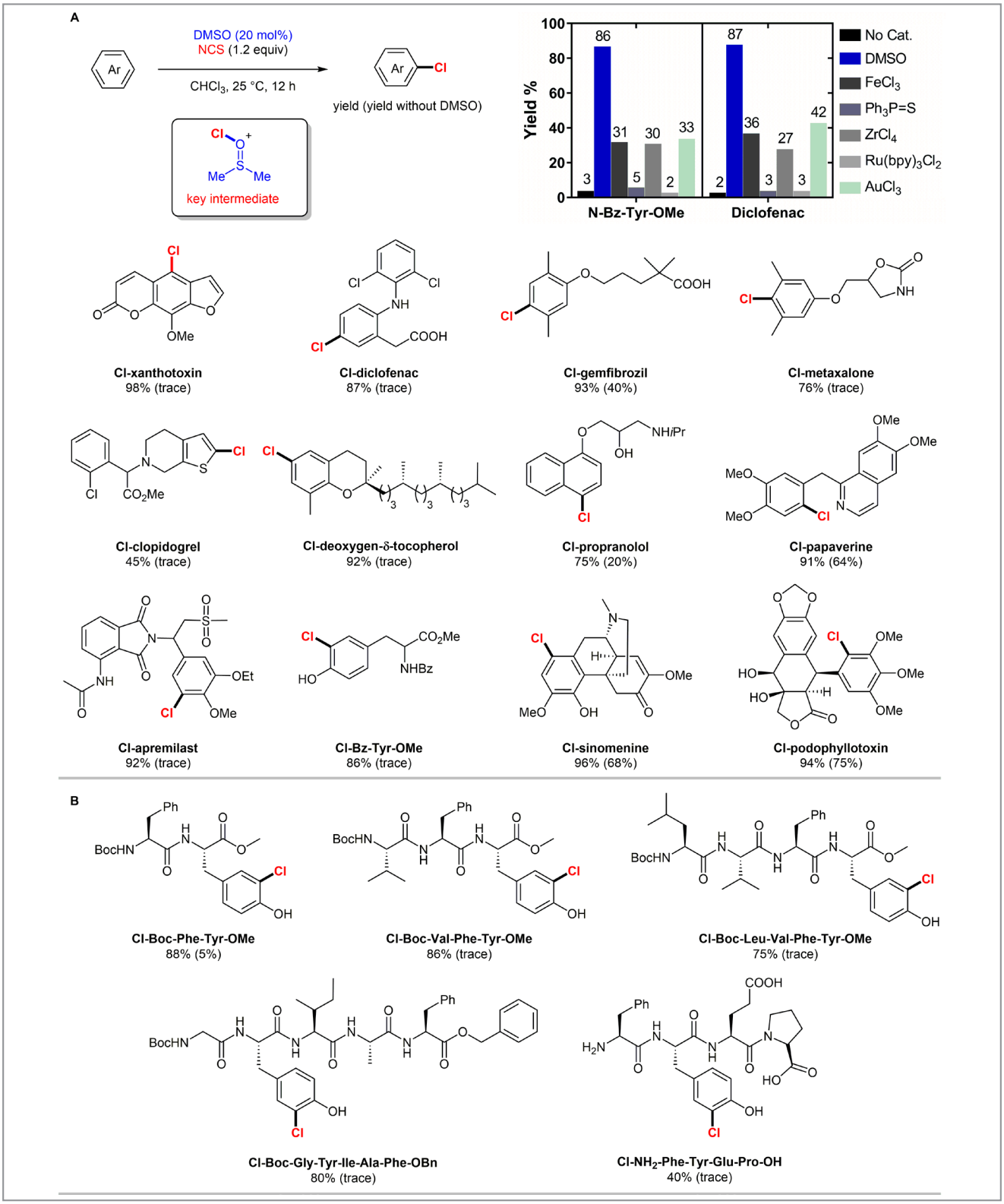
Previously, Professor Jiao's group had developed the HX/DMSO (X = Br, I) system for late-stage aromatic bromination and iodination of bioactive molecules, in which DMSO acted as a mild oxidant (*Org. Lett.* **2015**, *17*, 2886–2889). "The mild reaction conditions and operational simplicity make this method very attractive. Since its publication, the HX/DMSO halogenation system has been widely applied in total synthesis of natural products, halogenation of heteroarenes, and modification of bioactive molecules," remarked Professor Jiao. He continued: "After bromination and iodination, we investigated the oxidative chlorination of arenes with the HCl/DMSO system; unfortunately, the efficiency was very low because the electrode potential of Cl^+/Cl^- is higher than that of Br^+/Br^-." The failure of this oxidative approach motivated the group to develop other strategies that could lead to a mild and efficient late-stage chlorination of arenes.

During the study of aromatic bromination with HBr/DMSO, Professor Jiao's group found that the reaction rate increased if there was a slight excess of DMSO relative to HBr. "Since HBr is oxidized to bromonium ion *in situ*, we speculated that a suitable amount of DMSO may promote the halogenation. We reasoned that if that was actually the case, DMSO may be used as a Lewis base to catalyze the challenging chlorination," explained Professor Jiao. With the goal of proving this hypothesis, the group tested the chlorination of arenes with commercially available NCS as the chlorine source. "At the beginning of this study, the chlorination was performed with DMSO as the solvent," Professor Jiao said. "Unfortunately, only trace amounts of chlorination product were detected. Surprisingly, the chlorination of xanthotoxin, a natural product extracted from *Ammi majus* plant, afforded the product in 90% yield with 20 mol% of DMSO as the catalyst. Then, we achieved the late-stage chlorination of drugs and natural products (Scheme 1, A)." Gratifyingly, the group found that many functional groups, including –OH and -NH_2, could be perfectly tolerated in this system. These experiments indicated that the reactivity of NCS was strongly improved by DMSO, which made the chlorination possible. Moreover, the newly discovered DMSO catalysis was compared to some other reported Lewis acid and Lewis base promoted catalytic approaches. "For the chlorination of single amino acid N-Bz-Tyr-OMe and approved drug diclofenac, low efficiencies were obtained with other catalysts including $Ph_3P{=}S$, $FeCl_3$, $ZrCl_4$, $AuCl_3$ and $Ru(bpy)_3Cl_2$, respectively," noted Professor Jiao. He continued: "Conversely, these experiments revealed that DMSO catalysis featured high efficiency and good functional-group tolerance. In addition, this DMSO/NCS chlorination system performed very well on a multi-gram scale. Naproxen, gemfibrozil, and indole substrates were chlorinated in high yields, which shows great potential for industrial applications (up to 54.5 g)."

Professor Jiao noted that chemical modification of peptides or proteins has emerged as an invaluable tool in biochemistry (*Chem. Rev.* **2015**, *115*, 2174–2195). "Tyrosine is essential in proteins and many peptide drugs such as alarelin and oxytocin," he explained. "Importantly, a series of structurally diverse peptides with tyrosine residue could also be chlorinated efficiently by this novel DMSO catalytic protocol (Scheme 1, B). It is noteworthy that most of the chlorination reactions did not perform well in the absence of DMSO." This chemistry provides a practical synthetic protocol and shows great potential in biological applications, as well as in drug discovery and development, which also opens an avenue for further exploration and utilization of DMSO in organic synthesis.

Professor Jiao concluded: "An efficient late-stage chlorination of complex natural products, drugs, and peptides has been developed by our group. The very common and humble DMSO was disclosed as an efficient Lewis base catalyst. The strong polarization of DMSO makes the activation of chlorocation possible, thus enabling the chlorination process. Accordingly, our mechanistic studies revealed that the active DMSO·Cl+ was the key intermediate of this protocol."





Scheme 1 (A) Selected examples of DMSO-catalyzed late-stage chlorination. (B) Late-stage chlorination of peptides.

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