Asymmetric Cyanation of Acylated *N*-Heteroaromatic Compounds Using Ru–Li Combined Catalyst System

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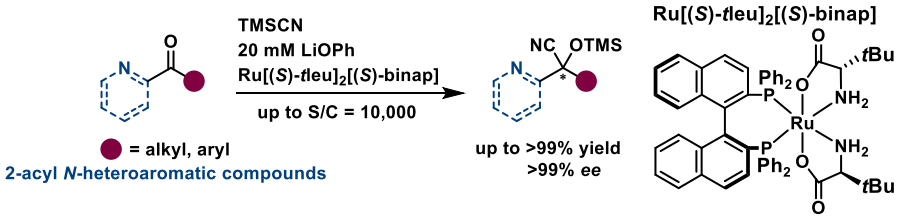
Catalytic asymmetric cyanation of ketones is an efficient method for constructing optically active cyanohydrins with quaternary carbon center, which serve as essential synthetic intermediates of natural compounds and pharmaceuticals.[1] One of the most important targets based on this background is cyanohydrins including *N*-heteroaromatic moieties. In 2007, Jacobsen and coworker reported a catalytic enantioselective cyanation of the simplest 2-acetylpyridine.[2] However, the approach requires a catalyst loading of 5 mol% and 12 hours reaction time, and this is the only reported example. We previously reported asymmetric cyanosilylation of various ketones catalyzed by Ru–Li combined system.[3,4] Chiral Ru(II)/diphosphine/amino acidate complex was the critical precursor of catalytic active species for the asymmetric cyanation. Building on these findings, we successfully developed an asymmetric cyanosilylation of 2-acylated *N*-heteroaromatic compounds.

Initially, 2-acetylpyridine was selected as the model substrate with trimethylsilyl cyanide (TMSCN) serving as the cyanide source. The combination of Ru(II)/(*S*)-BINAP/(*S*)-*t*-Leucinate and LiOPh was found to be the most suitable to the reaction: The cyanated product was obtained with >99% yield and 99% ee in 5-hour reaction at a substrate-to-catalyst molar ratio (S/C) of 500. Even with an extremely low catalyst loading of S/C = 10,000, the reaction completed without loss of enantioselectivity. Notably, 2-benzoylpyridine delivered exceptional results (>99% yield, >99% ee), despite the minimal steric differences between its aromatic substituents. The reaction is applicable not only to the 2-acylpyridines, but also to other 2-acyl *N*-heteroaromatic compounds including pyrazine, pyrimidine, quinoline, isoquinoline, and thiazole.



1) N. Kurono, T. Ohkuma *ACS. Catal*. **2016**, *6*, 989−1023. 2) E. N. Jacobsen, S. J. Zuend. *J. Am. Chem. Soc.* **2007**, *129*, 15872−15883. 3) N. Kurono, M. Uemura, T. Ohkuma *Eur. J. Org. Chem.* **2010**, *2010*, 1455–1459. 4) T. Ohkuma, N. Kurono, Y. Sakaguchi, K. Yamauchi, T. Yurino *Adv. Synth. Catal.* **2018**, *360*, 1517–1522.