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Ru(II)-Catalyzed Asymmetric Transfer Hydrogenation of Aryl(1-aryl-1*H*-1,2,3-triazol-4-yl)methanones: A Novel Strategy for Developing CFTR traffic Correctors

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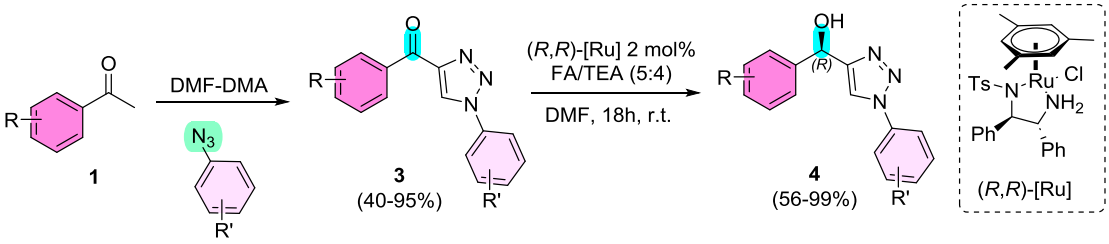
ABSTRACT

The aryl(1-aryl-1*H*-1,2,3-triazol-4-yl)methanols (**4**) have emerged as promising correctors of the misfolding of F508del-CFTR protein, the main mutation of cystic fibrosis.[1] Among the evaluated compounds, the racemic compound (*rac*)-**4b** exhibited the lowest EC_{50} value (1.70 µM). Subsequent evaluation of the enantiomers (*R*)- and (S)-**4b** revealed inactivity for one of them. To address this, a direct and practical method for the enantioselective synthesis of **4** was developed based on the Ru(II)-catalyzed the asymmetric transfer hydrogenation (ATH) of **3** (**Scheme 1**). [2] After optimization of the reaction conditions, ten substrates underwent ATH using 2 mol% of (*R*,*R*)-[Ru]. The conversion and observed enantiomeric excess (ee) were strongly influenced by substituent effects, with electron-donating or weakly donating groups in the ortho position to the carbonyl resulting in the highest ee (**Scheme 1**).



4a R= 2-Br; R'= 4-Br (92% conv., 80% ee)
4b R= 4-Br; R'= 4-Br (99% conv., 52% ee)
4c R= 4-Br; R'= 4-SCH_3 (56% conv., 36% ee)
4d R= 4-Br; R'= 4-CO_2H (*ND*)
4e R= 2-OMe; R'= 4-Br (77% conv., 82% ee)
4f R= 2,4-OMe; R'= 4-Br (58% conv., 80% ee)
4g R= 2-OH,4-OMe; R'= 4-Br (99% conv., 76% ee)
4h R= 2,4-OH; R'= 4-Br (94% conv., 78% ee)
4i R= 3,4,5-OMe; R'= 4-Br (96% conv., 50% ee)
4j R= 4-NO_2; R'= 4-Br (99% conv., 3% ee)

Scheme 1: Enantioselective synthesis of aryl(1-aryl-1*H*-1,2,3-triazol-4-yl)methanols

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