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Supporting Information

Direct oxidative amidation of aromatic aldehydes using aqueous hydrogen peroxide in continuous flow microreactor systems

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Experimental Details and Sample Analysis

All the reactions were carried out in a continuous flow system using a spiral-channel silicon-Pyrex microreactor with a total volume of 230 μL. The general experimental procedure is as follows. Two reactant solutions loaded in separate 2.5 mL syringes (Hamilton, GasTight) were delivered into the microreactor through the two inlet ports via Teflon tubings (Upchurch, 0.02 in. i.d.) with the same infusion rate that is controlled by a syringe pump (Harvard Apparatus, 9801781). Typically, one solution contained aldehyde (1 mol/L), aqueous hydrogen peroxide (1.2 mol/L), *p*-xylene as the internal standard (0.5 mol/L), and acetonitrile (or *tert*-butanol), and the other contained amine and acetonitrile (or *tert*-butanol), the concentration of amine being varied for reaction optimization. The residence time control (10-100 min) was achieved by varying the flow rate of the reactants. The temperature of the reaction zone (60-140 ^{o}C) was monitored using a K-type thermocouple that was inserted into a small hole on the side of the packaging chuck and was controlled by a PID controller (Omega, CN7833) that was connected to the heating cartridges inserted into the chuck. The outlet port of the microreactor was connected to a 6-way injection valve (Upchurch, V-451) to collect product samples for chemical analysis. A high-pressure stainless steel vessel (Parr Instrument, N4714AB) was used to provide back pressure (N_2, 20-60 psi) to allow reactions to be operated at temperatures higher than the boiling point of the solvent and meanwhile collect the waste materials. A micro-metering needle valve connected to the outlet tubing was used to maintain a constant pressure inside the vessel.

The collected samples were analyzed using GC with an FID detector. To quantify the GC data, all peaks were normalized by dividing the area of a given peak by the area corresponding to the internal standard. The selectivities toward the amides were determined on the basis of the normalized peak areas for amides and other side products. The conversions were derived by comparing the difference in the normalized peak areas for the aldehydes in the solutions collected before the inlet port and at the outlet. The yields were calculated from the conversions and selectivites thus obtained. Amides were identified using GC-MS by comparing their parent ions and fragmentation patterns with the standard spectra. The enantiometric excess in the reaction of proline *tert*-butyl esters was determined using chiral HPLC.

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The product (Table 1, Entry 7) was isolated following a procedure described below. The reaction mixture was collected by combining 8 samples from the same stock solutions running continuously. Water was then added followed by extraction using dichloromethane. The organic layer was separated and concentrated under vacuum. Purification was performed with column chromatography (silica gel, dichloromethane:ethyl acetate 5:1) and the solvent was removed under vacuum to give light yellow crystals. Nuclear Magnetic Resonance spectra were obtained on a Bruker 400 MHz instrument with deuterated chloroform as the solvent. Chemical shifts of ^{1}H were relative to the residual chloroform and those of ^{13}C to deuterated chloroform. ^{1}H NMR: δ 3.25-3.96 (m, 8H), 7.29-7.35 (m, 4H); ^{13}C NMR: δ 67.0, 128.9, 129.1, 133.8, 136.2, 169.6.