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Abstract

Primary aliphatic amines which are ubiquitous in natural products, traditionally considered as inert to substitution reactions. Recent studies clearly demonstrated that the aliphatic deaminative coupling chemistry can be used to make valuable C(sp^3) synthons in various cross-coupling reactions proceeding through C–N bond activation on transition metal complexes. The catalytic system generated in situ from the tetranuclear Ru–H complex with a catechol ligand (**2-9**/**2-16**) and independently synthesized ruthenium catecholate complex **2-11** was found to be effective for the direct deaminative coupling of two primary amines to form secondary amines with high chemo-selective fashion. The catalytic system formed *in-situ* from the reaction of cationic Ru–H complex **2-10** with 3,4,5,6-tetrachloro-1,2-benzoquinone **2-12** was found to mediate a regioselective deaminative coupling reaction of ketones with amines to form the α-alkylated ketone products. Both benzylic and aliphatic primary amines were found to be suitable substrates for the coupling reaction with ketones in forming the α-alkylated ketone products. The coupling reaction with chiral amines led to a highly diastereoselective formation of the alkylation products. The monitoring of the coupling reaction of acetophenone and 4-methoxybenzylamine showed a rapid formation of $PhC(Me)=NCH_2C_6H_4$-4-OMe, which was slowly converted to the alkylation product. The coupling reaction of $PhCOCD_3$ with 4-methoxybenzylamine showed an extensive H/D exchange on both a-CH_2 (41% D) and b-CH_2 (21%) positions of the alkylation product. The Hammett plot obtained from the reaction of *para*-substituted imines *p*-X-$C_6H_4CH_2N=C(Me)C_6H_5$ (X = OMe, H, F, CF_3) showed a strong promotional effect by the amine substrates with electron-releasing group ($\rho = -0.96 \pm 0.1$), while the analogous plot obtained from the reaction of *para*-substituted imines *p*-Y-$C_6H_4C(Me)=NCH_2C_6H_4$-*p*-OMe (Y = OMe, H, F, CF_3) with benzylamine showed a moderate promotional effect from the ketone substrates with electron-withdrawing group ($\rho = +0.24 \pm 0.1$). The most significant carbon isotope effect was observed on the α-carbon of the alkylation product ($C_\alpha = 1.020$) from the coupling reaction of acetopheone with 4-methoxybenzylamine. The empirical rate law was determined as rate = k_{obs}[imine][Ru] from measuring the kinetics of the alkylation reaction of the isolated imine substrate. A catalytically active Ru-catecholate complex was synthesized from the reaction of the cationic Ru–H complex with 3,5-di-*tert*-butyl-1,2-benzoquinone and PCy_3. The DFT computational study revealed a stepwise mechanism of the [1,3]-carbon migration step via the formation of a Ru(IV)-alkyl species, which has a moderate activation enthalpy ($DH^‡$ = 44 kcal/mol). A plausible mechanism of the catalytic alkylation reaction via an intramolecular [1,3]-alkyl migration of Ru-enamine intermediate has been proposed on the basis of these experimental and computational data. The in situ formed ruthenium catalytic systems (**2-10**/**2-16**), (**2-10**/**2-12**) and complex **2-11** was also found to be highly selective for the dehydrogenative/deaminative coupling reactions of 2-aminophenyl ketones/2-aminobenzamides with amines/amino-acids to form number of pharmaceutically important nitrogen heterocyclic products. The catalytic coupling method provides an operationally simple and chemoselective synthetic protocol without using any reactive reagents or forming wasteful byproducts.