TAMING AMBIDENT TRIAZOLE NUCLEOPHILES: REGIOSELECTIVE ION-PAIRING AND PHASE-TRANSFER ORGANOCATALYSIS

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Controlling the regioselectivity of ambident nucleophiles towards simple alkylating agents is an enduring and fundamental problem throughout heterocyclic chemistry. Unsubstituted triazole nucleophiles pose a particularly vexing challenge in this arena [1, 2, 3]. By virtue of mechanistic insights garnered from ¹H NMR reaction monitoring, kinetic modelling, ¹H NMR-DOSY, X-ray crystallography, DLPNO-CCSD(T) computations and Marcus theory, we have developed an organocatalytic methodology for the direct *N*-alkylation of unsubstituted triazole anions that exhibits atypical regioselectivities. Our strategy exploits amidinium salts as phase-transfer catalysts, which shuttle triazole anions into solution through regioselective ion-pairing. The intimate ion-pairs formed in solution retain the reactivity of liberated triazole anions but exhibit regioselectivities that are completely inverted (1,2,4-triazole) or substantially enhanced (1,2,3-triazole), granting direct access to 4-alkyl-1,2,4-triazoles (*rr* = 88 - 94 %) and 1-alkyl-1,2,3-triazoles (*rr* = 95 - 99%) with excellent selectivities in one step.



Regioselectivity inverted by ion-pairing

^[1] P. G. Bulger, I. F. Cottrell, C. J. Cowden, A. J. Davies and U.-H. Dolling, *Tetrahedron Lett.*, **2000**, 41, 1297.

^[2] S. Ohta, I. Kawasaki, T. Uemura, M. Yamashita, T. Yoshioka and S. Yamaguchi, *Chem. Pharm. Bull.*, **1997**, 45, 1140.

^[3] X. Wang, D. Krishnamurthy, C. H. Senanayake and P. Wipf, Org. Lett., 2010, 12, 4632.