# Strathprints Institutional Repository

This version is available at http://strathprints.strath.ac.uk/58859/

# Contra-thermodynamic Hydrogen Atom Abstraction in the Selective C−H Functionalization of Trialkylamine *N*-CH₃ Groups

Joshua P. Barham,[†,‡] Matthew P. John,[‡] and John A. Murphy*,[†]

†WestCHEM, Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, United Kingdom

‡GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, United Kingdom

S *Supporting Information*

**ABSTRACT:** We report a simple one-pot protocol that affords functionalization of *N*-CH₃ groups in *N*-methyl-*N*,*N*-dialkyl-amines with high selectivity over *N*-CH₂R or *N*-CHR₂ groups. The radical cation DABCO⁺• , prepared in situ by oxidation of DABCO with a triarylaminium salt, effects highly selective and contra-thermodynamic C−H abstraction from *N*-CH₃ groups. The intermediates that result react in situ with organometallic nucleophiles in a single pot, affording novel and highly selective homologation of *N*-CH₃ groups. Chemoselectivity, scalability, and recyclability of reagents are demonstrated, and a mechanistic proposal is corroborated by computational and experimental results. The utility of the transformation is demonstrated in the late-stage site-selective functionalization of natural products and pharmaceuticals, allowing rapid derivatization for investigation of structure−activity relationships.



*Regio- and chemoselective single-pot functionalisation of trialkylamines with organometallics*

examples show up to 83% yield up to >30 : 1 *N*-CH₃ : *N*-CH₂
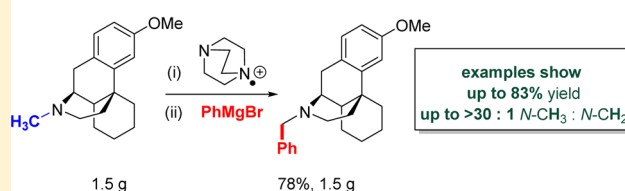
## INTRODUCTION

Site-selective functionalization of tertiary amines that bear an *N*-CH₃ group is of great importance to medicinal chemistry, where alterations reveal dramatic changes in activity. For example, transformation of the *N*-CH₃ group of oxymorphone (a μ-opioid agonist) into a cyclopropylmethyl group completely inverts pharmacological activity to yield the clinically useful μ-opioid antagonist, naltrexone (Scheme 1A).[1−3]

*N*-CH₃ functionalization is typically accomplished by stepwise N-demethylation followed by alkylation (Scheme 1B). These transformations are generally complex and require multiple chemical steps and can suffer variable selectivity or require toxic or expensive reagents.[4−13] Within opioid chemistry, stepwise approaches have been developed with mild reagents via iron-catalyzed N-demethylations of trialkylamine *N*-oxides, but selectivity is still variable and both N-oxidation and alkylation steps are required.[13−15] Hence *direct*, selective methods for functionalizing *N*-CH₃ groups of trialkylamines are desirable.

Recently, transition metal catalysis has contributed to the site-selective functionalization of tertiary amines.[16−19] Generally, these methods have shown selectivity for C−H activation remote from the nitrogen of a tertiary amine. Independently, the application of radical hydrogen atom transfer (HAT) to site-selective functionalization has made significant progress. MacMillan recently reported site-selective H atom transfer activations of *N*-Boc- and *N*-Bac-protected secondary amines and activations of alcohols as part of an overall photoredox transformation.[20,21] The intrinsic electronic properties of C−H bonds were exploited such that electrophilic (quinuclidinium-type) radical cations selectively engaged the most electron-rich

*N*-CH₂ positions. Where different alkyl groups were present in *N*-Bac-protected secondary amines, interesting selectivities began to emerge via HAT.[20]

In this paper, we announce that the radical cation DABCO⁺• achieves site-selective and contra-thermodynamic HAT reactions with trialkylamines that feature an *N*-CH₃ group. Following HAT, reactions yield metastable intermediates that react with organometallic reagents to afford *N*-CH₃-homologated products efficiently in a single pot (Scheme 1C).
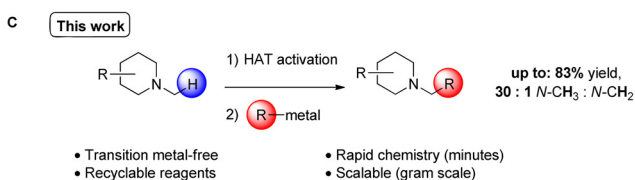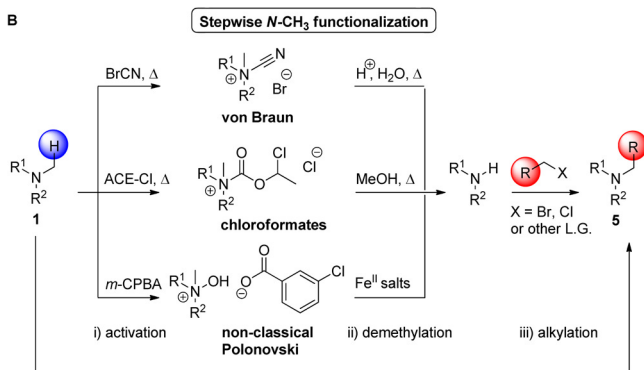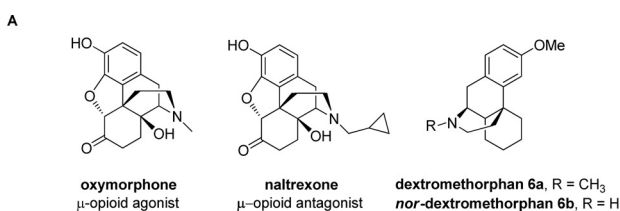
## RESULTS AND DISCUSSION

Initially, our mechanistic plan for the formation of desired products **5** was based on single electron oxidation of the trialkylamine nitrogen atom of the substrate and subsequent chemistry (Scheme 2A). Oxidation by single electron transfer (SET) gives rise to radical cation **2**. Deprotonation to afford α-amino radical **3** followed by further SET oxidation affords iminium salt **4**, primed for nucleophilic attack to yield homologated product **5**. This plan accords with expectations from photoredox[22−28] (and non-photoredox[29]) SET methods. Indeed, our initial efforts used photoredox catalysis conditions on dextromethorphan (**6a**) and led to unexpected results that will be reported elsewhere. Although SET methods are widely used, non-SET methods have also been used to functionalize trialkylamines.[30−33]

Jahn reported the use of tris(*p*-bromophenyl)aminium hexafluorophosphate (TBPA-PF₆) to oxidize trialkylamines **1** to N-radical cations **2**.[34] We wondered whether our substrates,

**Scheme 1. (A) Opioids, (B) Stepwise vs Direct N-CH₃ Functionalization Strategies, and (C) This Work**



**Table 1. N-CH₃ Functionalization of Dextromethorphan with a Variety of Organometallic Nucleophiles[a]**



| entry | R-metal | product | product yield (%) | recovered $p$-tol₃N (%) |
|---|---|---|---|---|
| 1 | Et-MgBr | 8 | 81 | 99 |
| 2 | allyl-I/In[b] | 9 | 71 | 99 |
| 3 | cyclopropyl-MgBr | 10 | 74 | 99 |
| 4 | vinyl-MgBr | 11 | 75 | 99 |
| 5 | Ph-MgBr | 12 | 83 | 99 |
| 6 | 4-pentenyl-MgBr | 13 | 57 | 99 |
| 7 | 3-butenyl-MgBr | 14 | 48 | ND |

[a]Isolated yields (%) after chromatography. ND (not determined). Aqueous workup instead of organometallic addition gave nor-dextromethorphan 6b (83%) and 7 (8%), thus selectivity was 10:1 in the oxidation step. [b]Allyl iodide (3.0 equiv) premixed with In powder (2.0 equiv).

**Scheme 2. (A) Mechanistic Plan for Oxidation of Trialkylamines and (B) Facile Synthesis of Stable Triarylaminium Radical Cation Salts**
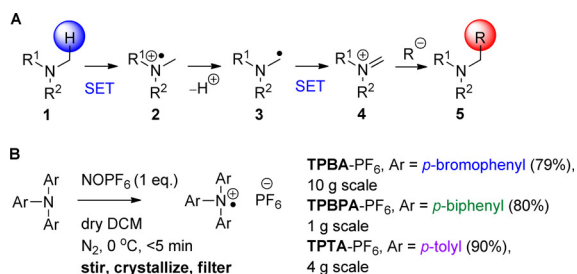


subjected to Jahn's conditions, would follow the proposed reaction pathway (Scheme 2A) to iminium salt 4. Our initial studies used TBPA-PF₆ [$E_{1/2}$ (tris(4-bromophenyl)amine) = +1.10 V vs saturated calomel electrode (SCE) in MeCN] as an oxidant for dextromethorphan (6a) ($E_{ox}^{p}$ (6a) = +0.89 V vs SCE in MeCN), selected as a chromophore-containing trialkylamine substrate which possessed N-CH₃, N-CH₂R, and N-CHR'R'' positions (Table 1).[35] Nor-dextromethorphan 6b (shown in Scheme 1) was detected by LCMS, supporting the intermediacy of an iminium salt. However, conversion was hampered by competitive S$_N$Ar-type reaction by the chosen base on the triarylaminium salt (see Supporting Information).[36] To overcome this, TBPA-PF₆ analogues were synthesized that do not feature leaving groups at the para-positions (Scheme 2B).[37]

Of these, TPTA-PF₆ ($E_{1/2}$ (tri-$p$-tolylamine) = +0.78 V vs SCE in MeCN) effected smooth conversion of dextromethorphan (6a) to a reactive intermediate which was intercepted by organometallic nucleophiles. Reaction optimization (see Supporting Information) identified conditions, TPTA-PF₆ (3.4 equiv), DABCO (4.5 equiv), and organometallic nucleophiles (5.0 equiv), to successfully transform 6a into N-alkyl-functionalized products (8–14) in good to excellent (48–83%) yields and high N-CH₃ regioselectivity (10:1) (Table 1). Interestingly, N-CH₂ functionalization operated as a minor pathway, giving rise ultimately to a DABCO-enamine byproduct 7 (see Supporting Information for proposed mechanism of formation), itself inert to the organometallic addition reaction.

Substrate scope of the TPTA-PF₆/DABCO-mediated C–H functionalization of trialkylamines is demonstrated in Scheme 3. In the syntheses of 15–28, chemo- and highly regioselective functionalization was observed in fair to high yields (48–81%) with the exception of 23 and 26. Remarkably, N-methyl-morpholine and benzyl-protected 1-methylpiperidin-4-ol gave exclusive (>30:1)[38] N-CH₃ functionalization to afford 16 and 22 in 77 and 81% yield, respectively.

The secondary alcohol in tropine was tolerated in the synthesis of 21, which contrasts with Ofial's $t$BuOOH-mediated α-cyanation of trialkylamines, which resulted in oxidation to the ketone.[33] Esters α and β to the trialkylamine were tolerated; in the synthesis of 19, no N-CH₂ functionalization was observed despite the stabilizing α-ester. Moving to substrates featuring highly electron-rich arenes, PMB-protected 1-methylpiperidin-4-ol gave exclusive selectivity (>30:1) at the trialkylamine for N-CH₃ functionalization, but competing para-methoxybenzyl cleavage resulted in an 18% yield of para-methoxybenzyl alcohol, in addition to 23% of the desired product (23) (starting material was recovered in 37% yield). This indicates competing SET oxidation of the PMB group. Interestingly, for N-methyl tetrahydroisoquinolines, complete reversal of regio-selectivity occurred, resulting in functionalization of the benzylic N-CH₂ to afford 24 and 25a in 59 and 72% yield, respectively, contrasting with the other trialkylamines.
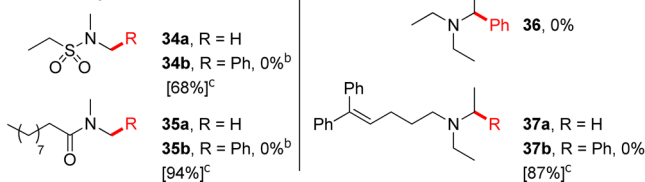
However, functionalization at the benzylic position is expected and is readily achieved in these cores.[24,28,30,31]

## Scheme 3. Regioselective C−H Functionalization of Trialkylamines[a]
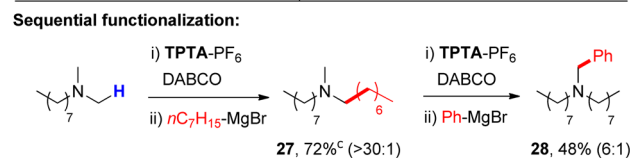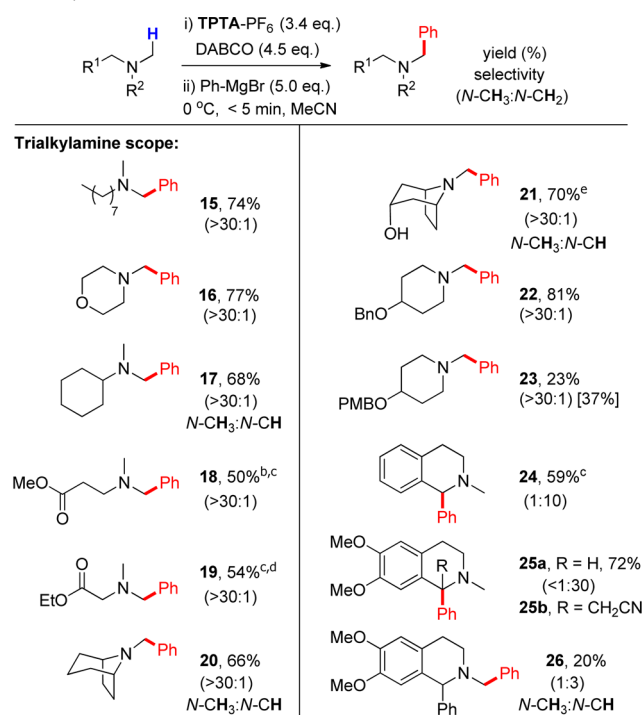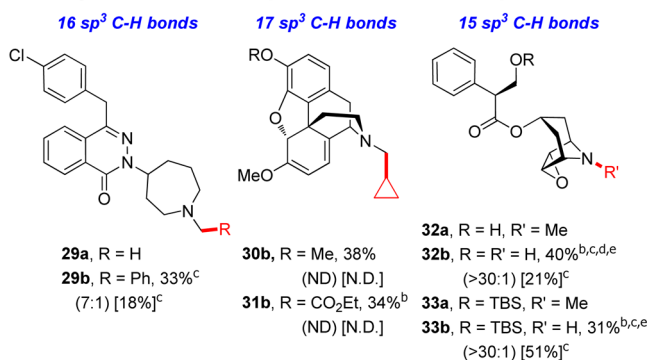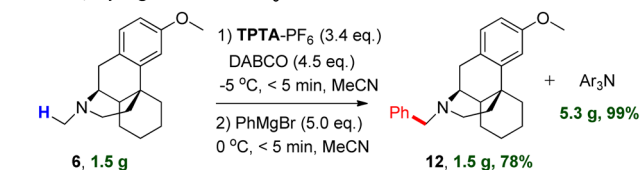


**Scheme 3. continued**

products as determined by ^{1}H NMR. ND (not determined). Phenylmagnesium bromide is used unless otherwise specified. [b]Phenylzinc halide used due to sensitive functional groups. [c]Yield of returned starting material, if detected, is given in square brackets. Yield determined by ^{1}H NMR. [d]An extra 1.0 equiv of sacrificial organometallic reagent used due to the free alcohol. [e]N-Demethylation was observed.
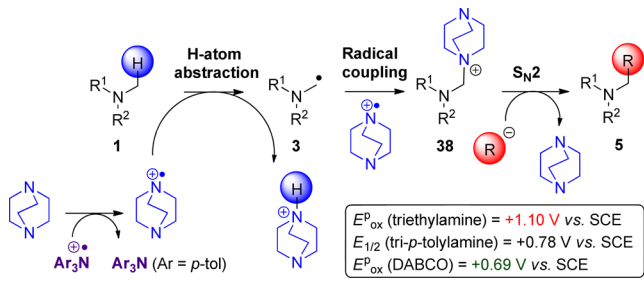
Subjecting the product **25a** to the reaction conditions resulted in $N$-CH functionalization to give an MeCN adduct **25b** in addition to the $N$-CH$_3$-functionalized product (**26**) ($N$-CH$_3$/$N$-CH = 1:3). Sequential functionalization of $N,N$-dimethyloctylamine was achieved, giving initially $N$-methyldioctylamine (**27**) in 72% yield (60% isolated yield) when the heptyl Grignard was employed. Functionalization of the remaining $N$-CH$_3$ group of $N$-methyldioctylamine (**27**) with the phenyl Grignard gave **28** in 48% yield. In this second reaction, the selectivity was noteworthy at 6:1 in favor of $N$-CH$_3$ functionalization, despite the statistical bias (1 × $N$-CH$_3$ vs 2 × $N$-CH$_2$ positions).

As examples of late-stage functionalization,[27] azelastine (**29a**), thebaine (**30a**, featuring an $N$-CH$_3$ group), and its carbonate derivative (**31a**, featuring an $N$-CH$_3$ group) were subjected to the reaction conditions and underwent successful $N$-CH$_3$ functionalization to **29b**, **30b**, and **31b**, respectively, albeit in diminished yields (33−38%). Interestingly, scopolamine (**32a**) and its protected analogue (**33a**) were also activated at the $N$-CH$_3$ group but gave N-demethylation products **32b** and **33b**. The sulfonamide and amide $N$-CH$_3$ groups of **34a** and **35a** were untouched by the reaction conditions, highlighting the selectivity of the reaction and its tolerance to electronically deactivated $N$-CH$_3$ groups. What was very striking was that trialkylamines containing only $N$-CH$_2$R positions gave no reaction under the conditions employed. Triethylamine gave no successful reaction to product **36**, but recovery and quantification of starting material was not possible. Therefore, we employed nonvolatile $N,N$-diethyl analogue **37a**, which gave no reaction. This observation markedly contrasts with previously reported trialkylamine functionalizations, which offered scope to engage trialkylamine $N$-CH$_2$R positions.[26,27,32,33]

A second observation is that, in general, excellent to exclusive selectivity (6:1 to >30:1) was observed for the $N$-CH$_3$ position over $N$-CH$_2$R or $N$-CHR$_2$ positions, with the highest levels of $N$-CH$_3$/$N$-CH$_2$ selectivity reported here competing with or exceeding those reported elsewhere. Even for noncyclic trialkylamines such as $N,N$-dimethyloctylamine and the most testing $N$-methyldioctylamine, **27**, selectivities were >30:1 and 6:1 in favor of $N$-CH$_3$ functionalization.

These two observations indicated that the transformation proceeds through a mechanism different from that shown in Scheme 2A. This led us to propose that successful reactivity and $N$-CH$_3$ selectivity are derived from the DABCO radical cation engaging in direct H atom transfer with the trialkylamine substrate (Scheme 4). Consistent with polarity-matching expectations, the electron-poor DABCO radical cation engages with the electron-rich α-amino C−H bonds.[20] Following HAT, we propose that the intermediate α-amino radical undergoes rapid trapping by a second molecule of DABCO radical cation to yield intermediate **38**.[39] We propose that metastable intermediate **38** undergoes an S$_N$2 reaction with an organo-
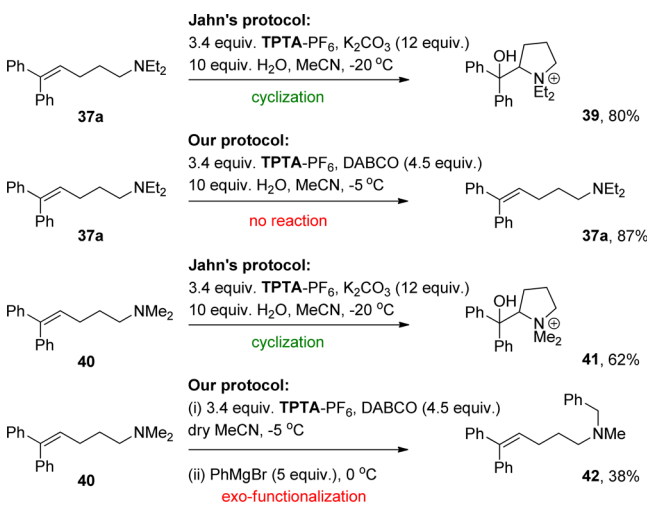
## Scheme 4. Proposed Mechanistic Pathway



These results show that our reactions do not proceed via the radical cations of our substrates.

Computation was used to probe selectivity ($N$-CH$_3$/$N$-CH$_2$) in the H atom abstraction step and the overall thermodynamic reaction profile (see Supporting Information and a previous computational study on H atom abstraction from amines[43]). For $N$-methylmorpholine (Figure 1), the product radical of
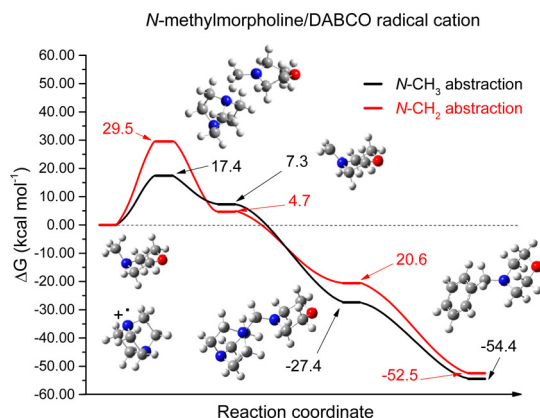


**Figure 1.** Reaction free energy ($\Delta G$) profile for $N$-CH$_3$ vs $N$-CH$_2$ H atom abstraction from $N$-methylmorpholine, formation of DABCO adduct intermediates and functionalized products. Key structures on the $N$-CH$_3$ functionalization reaction pathway are displayed.

metallic nucleophile to afford the $N$-CH$_3$-functionalized product. The nonreaction of soft nucleophiles (nitronates, silyl enol ethers, Cu-acetylides, and potassium trifluoroborates) ruled out a formal iminium salt as an intermediate, and $^1$H NMR studies of the reaction in MeCN-$d_3$ were consistent with **38** as the likely intermediate (see Supporting Information). We now outline experimental and computational evidence supporting a direct HAT mechanism.

First, we turned to Jahn's oxidative cyclization chemistry, where the intermediacy of N-radical cations is demonstrated via their rapid 5-*exo*-trig radical cyclizations.[34] Using TPTA-PF$_6$ as an oxidant under Jahn's conditions,[34] cyclization of **37a** occurred to afford **39** in 80% yield (Scheme 5). This confirms

## Scheme 5. Reactions of Radical Cation Reporter Substrates



that TPTA-PF$_6$ [$E_{1/2}$ (tri-$p$-tolylamine) = +0.78 V vs SCE] is capable of oxidizing trialkylamines ($E_{ox}^P$ (triethylamine) = +1.10 V vs SCE, $E_{ox}^P$ ($N$-methylmorpholine) = +1.10 V vs SCE) to N-radical cations, which accords with the closeness of redox potentials found by cyclic voltammetry.[40] However, under our $N$-CH$_3$ functionalization conditions where DABCO was present, substrate **37a** gave no reaction and an 87% recovery of starting material was observed.[41]

Therefore, DABCO must be oxidized faster than **37a**. This accords with cyclic voltammetry measurements (see Supporting Information), which show that DABCO ($E_{ox}^P$ = +0.69 V vs SCE) undergoes easier oxidation than triethylamine ($E_{ox}^P$ = +1.10 V vs SCE). Interestingly, when the analogous $N$,$N$-dimethyl-containing substrate **40** (shown to cyclize to give **41** under Jahn's conditions) was employed, $N$-CH$_3$ functionalization occurred to give **42** in 38% yield; no 5-*exo* (N-radical cation) or 6-*exo* ($\alpha$-amino radical) cyclization was observed.[42]

HAT from $N$-CH$_2$ (secondary radical) was more stable than that of HAT from $N$-CH$_3$ (primary radical) by 2.6 kcal mol$^{-1}$, as expected for the difference in energy between primary and secondary radicals (see Table 2). Interestingly, however, the

**Table 2. Difference in $\Delta G$ (TS) for a Range of Trialkylamine Substrates with Different HAT Agents and Experimental Selectivity[a]**

| HAT reaction | $\Delta\Delta G$ (TS) | $N$-CH$_3$/$N$-CH$_2$ |
|---|---|---|
| $N$-methylmorpholine/DABCO$^{+\bullet}$ | 12.1 | >30:1 |
| $N$-methylmorpholine/Me$_3$N$^{+\bullet}$ | 12.7 | |
| $N$-methylmorpholine/Me$^\bullet$ | 1.3 | |
| dextromethorphan (**6a**)/DABCO$^{+\bullet}$ | 2.7 | 10:1 |
| $N$-methyldioctylamine/DABCO$^{+\bullet}$ | 3.3 | 6:1 |
| $N$-methyldioctylamine/Me$^\bullet$ | 1.8 | |
| $N$-methyl THIQ/DABCO$^{+\bullet}$ | −2.6[b] | 1:10 |
| 6,7-dimethoxy-$N$-methyl THIQ/DABCO$^{+\bullet}$ | −3.8[b] | <1:30 |

[a]All starting materials, products, and transition state energies calculated using density functional theory calculations in Gaussian09 using an unrestricted B3LYP functional with a 6-31+G(d,p) basis set and C-PCM implicit solvent model.[45] All energies are in kcal mol$^{-1}$. [b]The transition state for $N$-CH$_2$R HAT is lower energy than $N$-CH$_3$ HAT.

transition state for HAT from $N$-CH$_3$ by a DABCO radical cation is a noteworthy 12.1 kcal mol$^{-1}$ lower in energy than the corresponding transition state for HAT from $N$-CH$_2$, in line with the experimental selectivity observed (>30:1). The resulting primary radical then follows a barrierless pathway to the $N$-methylmorpholine $N$-CH$_3$ DABCO adduct. Overall, $N$-CH$_3$ functionalization of $N$-methylmorpholine is exergonic ($\Delta G$ = −54.4 kcal mol$^{-1}$) with a 17.4 kcal mol$^{-1}$ barrier.[44] For amide **35a**, the barrier for HAT was 26.7 kcal mol$^{-1}$, consistent with the lack of reactivity observed experimentally (see Supporting Information).

Computation of the trimethylammonium radical cation as an H atom abstractor from *N*-methylmorpholine gave similar barriers and selectivity to the DABCO radical cation, whereas the methyl radical (a smaller HAT agent) behaved differently, giving much smaller activation energy differences for abstraction from *N*-CH$_3$ and *N*-CH$_2$ groups (Table 2). Computation of the open chain *N*-methyldioctylamine gave diminished selectivity, while computation of *N*-methyl tetrahydroisoquinolines (THIQs) predicted that the TS for *N*-CH$_2$ HAT would be lowest in energy. Overall, there is a strong relative correlation between the calculated $\Delta\Delta G$ (TS) and the experimental selectivity. Computational results and experimental observations suggest that steric factors are heavily implicated in the selectivity of the transformation. One steric factor is the hindrance around the trialkylamine substrate *N*-CH$_3$ and *N*-CH$_2$ positions.

An important steric factor is the structure of DABCO$^{+\bullet}$,[46] which sees the radical cation delocalized between the two nitrogen p-orbitals. As well as imparting stability to enhance the lifetime,[47,48] this results in a steric "cage" around the radical cation element, allowing DABCO$^{+\bullet}$ to be uniquely selective in its reactions.

## CONCLUSION

DABCO radical cation, generated in situ through the use of stable, rechargeable radical cation salts, engages in contra-thermodynamic HAT reactions with trialkylamines with exquisite regioselectivity for *N*-CH$_3$ groups. The least stable, primary $\alpha$-amino radicals are captured as metastable DABCO adduct intermediates which can be readily intercepted with hard nucleophiles (organometallics or water), facilitating N-functionalization in a single pot. The transformation is rapid and scalable and benefits from recyclable TPTA-PF$_6$. We foresee applications of this *direct* N-functionalization methodology in medicinal chemistry: in the late-stage functionalization of molecules or the investigation of structure–activity relationships.

## ASSOCIATED CONTENT

**Ⓢ Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09690.

> Experimental procedures including the synthesis of substrates, key NMR spectra, characterization data of novel compounds, cyclic voltammetry, EPR studies, and computational coordinates (PDF)

## AUTHOR INFORMATION

**Corresponding Author**

*john.murphy@strath.ac.uk

**ORCID** Ⓘ

John A. Murphy: 0000-0003-3136-0845

**Notes**

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

## REFERENCES

(1) Endoma-Arias, M. A. A.; Cox, D. P.; Hudlicky, T. *Adv. Synth. Catal.* **2013**, *355*, 1869−1873.
(2) Prommer, E. *Supp. Care Cancer* **2006**, *14*, 109−115.
(3) Deer, T. R.; Leong, M. S.; Buvanendran, A.; Gordin, V.; Kim, P. S.; Panchal, S. J.; Ray, A. L. *Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches*, 1st ed.; Springer: New York, 2013.
(4) von Braun, J. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2035−2057.
(5) von Braun, J. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1252−1260.
(6) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, *18*, 1567−1570.
(7) Olofson, R. A.; Martz, J. T. *J. Org. Chem.* **1984**, *49*, 2081−2082.
(8) Santamaria, J.; Ouchabane, R.; Rigaudy, J. *Tetrahedron Lett.* **1989**, *30*, 3977−3980.
(9) McCamley, K.; Ripper, J. A.; Singer, R. D.; Scammells, P. J. *J. Org. Chem.* **2003**, *68*, 9847−9850.
(10) Dong, Z.; Scammells, P. J. *J. Org. Chem.* **2007**, *72*, 9881−9885.
(11) Werner, L.; Machara, A.; Adams, D. R.; Cox, D. P.; Hudlicky, T. *J. Org. Chem.* **2011**, *76*, 4628−4634.
(12) Mary, A.; Renko, D. Z.; Guillou, C.; Thal, C. *Tetrahedron Lett.* **1997**, *38*, 5151−5152.
(13) Kok, G. B.; Pye, C. C.; Singer, R. D.; Scammells, P. J. *J. Org. Chem.* **2010**, *75*, 4806−4811.
(14) Polonovski, M.; Polonovski, M. *Bull. Soc. Chim. Fr.* **1927**, *41*, 1190−1208.
(15) Ferris, J. P.; Gerwe, R. D.; Gapski, G. R. *J. Org. Chem.* **1968**, *33*, 3493−3498.
(16) Li, Q.; Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 8755−8765.
(17) Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. *Nature* **2016**, *531*, 220−224.
(18) Mbofana, C. T.; Chong, E.; Lawniczak, J.; Sanford, M. S. *Org. Lett.* **2016**, *18*, 4258−4261.
(19) Nako, A. E.; Oyamada, J.; Nishiura, M.; Hou, Z. *Chem. Sci.* **2016**, *7*, 6429−6434.
(20) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; Macmillan, D. W. C. *Science* **2016**, *352*, 1304−1308. One example demonstrated an *N*-CH$_3$ vs *N*-CH$_2$ selectivity of 4:1.
(21) Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C. *Science* **2015**, *349*, 1532−1536.
(22) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464−1465.
(23) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94−97.
(24) Barham, J. P.; John, M. P.; Murphy, J. A. *Beilstein J. Org. Chem.* **2014**, *10*, 2981−2988.
(25) Rueping, M.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C.; Leonori, D.; Vila, C. *Chem. - Eur. J.* **2012**, *18*, 5170−5174.
(26) Xie, J.; Shi, S.; Zhang, T.; Mehrkens, N.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 6046−6050.
(27) Xie, J.; Yu, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 9416−9421.
(28) Fu, W.; Guo, W.; Zou, G.; Xu, C. *J. Fluorine Chem.* **2012**, *140*, 88−94.
(29) Richter, H.; Fröhlich, R.; Daniliuc, C.-G.; García Mancheño, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 8656−8660.
(30) Jones, K. M.; Karier, P.; Klussmann, M. *ChemCatChem* **2012**, *4*, 51−54.
(31) Singh, K. N.; Kessar, S. V.; Singh, P.; Singh, P.; Kaur, M.; Batra, A. *Synthesis* **2014**, *46*, 2644−2650.
(32) Allen, J. M.; Lambert, T. H. *J. Am. Chem. Soc.* **2011**, *133*, 1260−1262.
(33) Wagner, A.; Ofial, A. R. *J. Org. Chem.* **2015**, *80*, 2848−2854.
(34) Jahn, U.; Aussieker, S. *Org. Lett.* **1999**, *1*, 849−852.

(35) The conditions reported by Huo in the catalytic oxidation of N-substituted tetrahydroisoquinolines failed to give any significant conversion with dextromethorphan (**6a**) as a substrate (see Supporting Information): Huo, C. *J. Org. Chem.* **2014**, *79*, 9860−9864.

(36) This reaction pathway has been previously documented by Engel and Eberson, who observed reaction of TBPA salts with 2,3-diazabicyclo[2.2.2]oct-2-ene and acetate anion, respectively. Engel, P. S. *J. Am. Chem. Soc.* **1988**, *110*, 7880−7882. Eberson, L. *Acta Chem. Scand.* **1989**, *43*, 698−701.

(37) TPTA-PF$_6$ and TPBPA-PF$_6$ exist as strongly colored crystalline solids that are air-stable and can be stored in a refrigerator for months without any depreciation of activity.

(38) For selectivities >30:1, the minor component could not be detected in the $^1$H NMR spectrum of the crude reaction products.

(39) We cannot rule out rapid oxidation of the $\alpha$-amino radical to the iminium ion that is trapped by DABCO nucleophilically.

(40) On the basis of redox potentials, the oxidation of trialkylamines by TPTA-PF$_6$ appears to be endergonic (+0.3 V). Precipitation of tri-*p*-tolylamine may assist the reaction. this is observed in MeCN during the oxidation reaction.

(41) If DABCO is absent at the start and TPTA-PF$_6$ (3.4 equiv) and DABCO (4.5 equiv) are added portionwise, **39** is observed in 28% yield.

(42) Despite the diminished yield, **42** was observed as the sole substrate-derived component in the $^1$H NMR spectrum of the crude reaction products.

(43) Salamone, M.; Dilabio, G. A.; Bietti, M. *J. Org. Chem.* **2011**, *76*, 6264−6270.

(44) Reactions with a 20 kcal mol$^{-1}$ barrier proceed spontaneously at rt. At 25 °C, a fraction of $2.21 \times 10^{-15}$ molecules have energies exceeding the activation energy according to the Boltzmann distribution. This translates to barriers of 18 kcal mol$^{-1}$, leading to spontaneous reactions at −5 °C.

(45) (a) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864−B871. (b) Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, *140*, A1133−A1138. (c) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukada, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N. .; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Gaussian Inc.: Wallingford, CT, 2009. (d) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (e) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995−2001. (f) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669−681.

(46) McKinney, T. M.; Geske, D. H. *J. Am. Chem. Soc.* **1965**, *87*, 3013−3014.

(47) Zheng, Z.-R.; Evans, D. H.; Nelsen, S. F. *J. Org. Chem.* **2000**, *65*, 1793−1798.

(48) Kim, D.; Scranton, A. B.; Stansbury, J. W. *J. Appl. Polym. Sci.* **2009**, *114*, 1535−1542.