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Diversification of unprotected alicyclic amines via C–H bond functionalization: Decarboxylative alkylation of transient imines

Anirudra Paul,^{[a],+} Jae Hyun Kim,^{[a],+} Scott D. Daniel,^[a] and Daniel Seidel^{[a],+}

Abstract: Despite extensive efforts by many practitioners in the field, methods for the direct α -C–H bond functionalization of unprotected alicyclic amines remain rare. A new advance in this area utilizes Nlithiated alicyclic amines. These readily accessible intermediates are converted to transient imines through the action of a simple ketone oxidant, followed by alkylation with a β -ketoacid under mild conditions to provide valuable β -amino ketones with unprecedented ease. Regioselective α' -alkylation is achieved for substrates with existing α substituents. The method is further applicable to the convenient onepot synthesis of polycyclic dihydroquinolones through the incorporation of a S_NAr step.

Driven largely by the importance of this class of compounds in synthetic and medicinal chemistry,^[1] the synthesis of substituted alicyclic amines by means of C-H bond functionalization remains a highly active area of research.^[2,3] In stark contrast to the numerous advances that have been achieved with 3° or protected 2° amines, highly desirable methods for the direct synthesis of αfunctionalized 2° (i.e. unprotected) alicyclic amines from their corresponding parent amines remain limited (Scheme 1).[3],4] Moreover, α'-C-H bond functionalization of 2° alicyclic amines with an existing α -substituent is exceptionally challenging,^[3],5,6] especially with electronically activating substituents that favor functionalization at the substituted site. Leveraging the known ability of lithium amides to generate imines upon reaction with simple ketone oxidants (e.g., $1 \rightarrow 2$, Scheme 1),^[7] we recently developed a new method for the C-H bond functionalization of unprotected alicyclic amines.[8] Specifically, transient cyclic imines 2 generated from the oxidation of lithium amides 1 engage organolithium nucleophiles to provide a-functionalized products. Regioselective a'-C-H bond functionalization of a-substituted alicyclic amines was also achieved.[8a] The scope of the nucleophile could be expanded to other organometallics such as Grignard reagents by using Lewis acids to activate the imine intermediates.^[8b] However, α '-C-H bond functionalization of α substituted amines proved to be incompatible with Lewis acid activation, hampering our efforts to further expand the scope of nucleophiles. Particularly attractive would be new methods in which a'-C-H bond functionalization is achieved with nonorganometallic nucleophiles. Here we report an approach for the rapid diversification of transient imines 2 via decarboxylative

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alkylation with β -ketoacids **3** to provide β -aminoketones **4**. In addition, utilizing o-fluoroaryl- β -ketoacids **5**, polycyclic amines **6** can be obtained in a single operation via a process that involves a subsequent S_NAr reaction.





Decarboxylative and regioselective alkylation of transient imines (this work):







Scheme 1. Overview of methods for the C–H bond functionalization of amines and present strategy.

Mannich reactions and their decarboxylative variants employing β -keto acids represent valuable tools for the synthesis of β -amino ketones from imines.^[9-11] Despite the utility of the corresponding products, the use of enolizable cyclic imines in these reactions has largely remained limited to easily accessible alicyclic imines such as 1-pyrroline and 1-piperideine. $^{\left[12-15\right] }$ This is likely the result of the limited availability/stability of enolizable cyclic imines, in particular chiral variants possessing a substituent in the a-position. In order to determine whether the in-situgeneration of alicyclic imines via lithium amide oxidation is compatible with the decarboxylative Mannich process, we evaluated a range of reaction conditions. Key findings with the model substrates piperidine and β -keto acid 3a are summarized in Scheme 2. Following amine deprotonation and treatment with trifluoroacetophenone to rapidly access 1-piperideine, β-keto acid 3a (1.5 equiv) was added, followed by stirring at room temperature. Desired β-amino ketone 4a was obtained in 39% yield. The yield of 4a could be increased to 50% by employing 2.5 equivalents of 3a. Considering that the Li-alkoxide resulting from the reduction of trifluoroacetophenone may interfere with the subsequent decarboxylative alkylation,¹⁶ the addition of acidic additives was explored. Indeed, small to appreciable improvements in yield were observed in all cases. Trifluoroacetic

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acid (TFA) outperformed acetic acid as an additive, presumably because lithium acetate is still sufficiently basic to partially impede the addition process. Under the optimized conditions, product **4a** was obtained in 76% yield.



Scheme 2. Selected optimization reactions.

The scope of the reaction was explored with a broad range of alicyclic amines and β -keto acids (Scheme 3). Different ring sizes and substitution patterns on both reaction partners were readily accommodated. Both aryl and alkyl ketones could be introduced. Synthetically useful yields of β -amino ketones **4** were obtained in most cases. Particularly useful are reactions with amines that contain α -substituents. Regioselective substitution of the α' -position was observed in all cases. Diastereoselectivities ranged from poor to excellent (vide infra). Using o-fluoroaryl- β -keto acids **5** and adding an S_NAr step without the need for isolating intermediates enabled the efficient preparation of various polycyclic dihydroquinolones **6**. These species, which are now available directly from their unfunctionalized amines, are rather challenging to prepare by other means.^[17,18]



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As shown in Scheme 3, products 4p-4y were obtained predominantly as trans-diastereomers. The trans-diastereomers are in fact the kinetic products of these reactions, as it has been the corresponding established that cis-isomers are thermodynamically more stable.^[19] Interconversion of the diastereomers is possible, presumably via a retro-Mannich or retro-conjugate addition pathway. Indeed, simply changing the reaction conditions in the synthesis of product 4p allowed for a complete reversal of diastereoselectivity in favor of the cisisomer (Scheme 4).

i) n-BuLi (1 equiv), ether, -78 °C, 5 min ii) PhCOCF₃ (1.7 equiv), -78 °C, 5 min iii) TFA (1.05 equiv) in THF, 5 min iv) 3a (1.5 equiv), -78 °C; then rt for 2 h v) Solvent removal; then MeOH, rt, 22.5 h

Scheme 4. Formation of cis-product.

In summary, we have achieved the α -alkylation of unprotected alicyclic amines via a decarboxylative Mannich process involving regioselective C–H bond functionalization. Adding an S_NAr step to the overall reaction sequence, this process was further extended to the synthesis of polycyclic dihydroquinolones in a single operation.

(±)-4p, 65%, dr = 13:1

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Keywords: C–H bond functionalization • alicyclic amines • decarboxylative C–C bond formation • Mannich reaction • annulation

- a) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* 2014, *57*, 5845; b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* 2014, *57*, 10257.
- Selected recent reviews on amine C-H bond functionalization: a) K. R. [2] Campos, Chem. Soc. Rev. 2007, 36, 1069; b) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, Chem. Eur. J. 2010, 16, 2654; c) C. S. Yeung, V. M. Dong, Chem. Rev. 2011, 111, 1215; d) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, Chem. Eur. J. 2012, 18, 10092; e) K. M. Jones, M. Klussmann, Synlett 2012, 23, 159; f) B. Peng, N. Maulide, Chem. Eur. J. 2013, 19, 13274; g) S. A. Girard, T. Knauber, C.-J. Li, Angew. Chem. Int. Ed. 2014, 53, 74; h) M. C. Haibach, D. Seidel, Angew. Chem. Int. Ed. 2014, 53, 5010; i) L. Wang, J. Xiao, Adv. Synth. Catal. 2014, 356, 1137; j) C.-V. T. Vo, J. W. Bode, J. Org. Chem. 2014, 79, 2809; k) D. Seidel, Org. Chem. Front. 2014, 1, 426; I) Y. Qin, J. Lv, S. Luo, Tetrahedron Lett. 2014, 55, 551; m) D. Seidel, Acc. Chem. Res. 2015, 48, 317; n) J. W. Beatty, C. R. J. Stephenson, Acc. Chem. Res. 2015, 48, 1474; o) S. Mahato, C. K. Jana, Chem. Rec. 2016, 16, 1477; p) Y. Qin, L. Zhu, S. Luo, Chem. Rev. 2017, 117, 9433; q) M.-X. Cheng, S.-D. Yang, Synlett 2017, 28, 159; r) J. C. K. Chu, T. Rovis, Angew. Chem. Int. Ed. 2018, 57, 62; s) L. Gonnard, A. Guérinot, J. Cossy, Tetrahedron 2019, 75, 145; t) S. Liu, Z. Zhao, Y. Wang, Chem. Eur. J. 2019, 25, 2423; u) D. Antermite, J. A.

Bull, *Synthesis* **2019**, *51*, 3171; v) A. Trowbridge, S. M. Walton, M. J. Gaunt, *Chem. Rev.* **2020**, *120*, 2613.

- Selected recent examples of mechanistically diverse methods for amine [3] C-H bond functionalization: a) Z. Zhao, Y. Luo, S. Liu, L. Zhang, L. Feng, Y. Wang, Angew. Chem. Int. Ed. 2018, 57, 3792; b) F. Wang, M. Rafiee, S. S. Stahl, Angew. Chem. Int. Ed. 2018, 57, 6686; c) S. Greßies, F. J. R. Klauck, J. H. Kim, C. G. Daniliuc, F. Glorius, Angew. Chem. Int. Ed. 2018, 57, 9950; d) R. J. Griffiths, W. C. Kong, S. A. Richards, G. A. Burley, M. C. Willis, E. P. A. Talbot, Chem. Sci. 2018, 9, 2295; e) F. I. M. Idiris, C. E. Majeste, G. B. Craven, C. R. Jones, Chem. Sci. 2018, 9, 2873; f) S.-S. Li, X. Lv, D. Ren, C.-L. Shao, Q. Liu, J. Xiao, Chem. Sci. 2018, 9, 8253; g) A. F. G. Maier, S. Tussing, H. Zhu, G. Wicker, P. Tzvetkova, U. Flörke, C. G. Daniliuc, S. Grimme, J. Paradies, Chem. Eur. J. 2018, 24, 16287; h) K. Mori, R. Isogai, Y. Kamei, M. Yamanaka, T. Akiyama, J. Am. Chem. Soc. 2018, 140, 6203; i) M. Shang, J. Z. Chan, M. Cao, Y. Chang, Q. Wang, B. Cook, S. Torker, M. Wasa, J. Am. Chem. Soc. 2018, 140, 10593; j) A. J. J. Lennox, S. L. Goes, M. P. Webster, H. F. Koolman, S. W. Djuric, S. S. Stahl, J. Am. Chem. Soc. 2018, 140, 11227; k) J. Zhang, S. Park, S. Chang, J. Am. Chem. Soc. 2018, 140, 13209; I) A. M. Nauth, E. Schechtel, R. Dören, W. Tremel, T. Opatz, J. Am. Chem. Soc. 2018, 140, 14169; m) H.-J. Jiang, X.-M. Zhong, J. Yu, Y. Zhang, X. Zhang, Y.-D. Wu, L.-Z. Gong, Angew. Chem. Int. Ed. 2019, 58, 1803; n) M. A. Ashley, C. Yamauchi, J. C. K. Chu, S. Otsuka, H. Yorimitsu, T. Rovis, Angew. Chem. Int. Ed. 2019, 58, 4002; o) S. Guin, P. Dolui, X. Zhang, S. Paul, V. K. Singh, S. Pradhan, H. B. Chandrashekar, S. S. Anjana, R. S. Paton, D. Maiti, Angew. Chem. Int. Ed. 2019, 58, 5633; p) W. G. Whitehurst, J. H. Blackwell, G. N. Hermann, M. J. Gaunt, Angew. Chem. Int. Ed. 2019, 58, 9054; q) Y. Ma, X. Yao, L. Zhang, P. Ni, R. Cheng, J. Ye, Angew. Chem. Int. Ed. 2019, 58, 16548; r) R. Grainger, T. D. Heightman, Steven V. Ley, F. Lima, C. N. Johnson, Chem. Sci. 2019, 10, 2264; s) D. Vasu, A. L. Fuentes de Arriba, J. A. Leitch, A. de Gombert, D. J. Dixon, Chem. Sci. 2019, 10, 3401; t) S. Asako, S. Ishihara, K. Hirata, K. Takai, J. Am. Chem. Soc. 2019, 141, 9832; u) W. Lin, K.-F. Zhang, O. Baudoin, Nat. Catal. 2019, 2, 882; v) J. Z. Chan, Y. Chang, M. Wasa, Org. Lett. 2019, 21, 984; w) L. Zhou, Y.-B. Shen, X.-D. An, X.-J. Li, S.-S. Li, Q. Liu, J. Xiao, Org. Lett. 2019, 21, 8543; x) M. Kataoka, Y. Otawa, N. Ido, K. Mori, Org. Lett. 2019, 21, 9334; y) M. Lee, A. Adams, P. B. Cox, M. S. Sanford, Synlett 2019, 30, 417; z) M. Kapoor, P. Chand-Thakuri, J. M. Maxwell, D. Liu, H. Zhou, M. C. Young, Synlett 2019, 30, 519: aa) K. Ohmatsu, R. Suzuki, Y. Furukawa, M. Sato, T. Ooi, ACS Catal. 2020, 10, 2627; ab) J. B. Roque, Y. Kuroda, J. Jurczyk, L.-P. Xu, J. S. Ham, L. T. Göttemann, C. A. Roberts, D. Adpressa, J. Saurí, L. A. Joyce, D. G. Musaev, C. S. Yeung, R. Sarpong, ACS Catal. 2020, 10, 2929; ac) A. W. Rand, H. Yin, L. Xu, J. Giacoboni, R. Martin-Montero, C. Romano, J. Montgomery, R. Martin, ACS Catal. 2020, 10, 4671; ad) W. Liu, T. Babl, A. Röther, O. Reiser, H. M. L. Davies, Chem. Eur. J. 2020, 26, 4236; ae) P. Verma, J. M. Richter, N. Chekshin, J. X. Qiao, J.-Q. Yu. J. Am. Chem. Soc. 2020, 142, 5117; af) M. M. Walker, B. Koronkiewicz, S. Chen, K. N. Houk, J. M. Mayer, J. A. Ellman, J. Am. Chem. Soc. 2020, 142, 8194; ag) K. Feng, R. E. Quevedo, J. T. Kohrt, M. S. Oderinde, U. Reilly, M. C. White, Nature 2020, 580, 621; ah) P. J. Sarver, V. Bacauanu, D. M. Schultz, D. A. DiRocco, Y.-h. Lam, E. C. Sherer, D. W. C. MacMillan, Nat. Chem. 2020, 12, 459; ai) J. B. McManus, N. P. R. Onuska, M. S. Jeffreys, N. C. Goodwin, D. A. Nicewicz, Org. Lett. 2020, 22, 679; aj) R. Oeschger, B. Su, I. Yu, C. Ehinger, E. Romero, S. He, J. Hartwig, Science 2020, 368, 736; ak) M. A. Short, J. M. Blackburn, J. L. Roizen, Synlett 2020, 31, 102; al) A. S. H. Ryder, W. B. Cunningham, G. Ballantyne, T. Mules, A. G. Kinsella, J. Turner-Dore, C. M. Alder, L. J. Edwards, B. S. J. McKay, M. N. Grayson, A. J. Cresswell, Angew. Chem. Int. Ed. 2020, 59, 14986.
- [4] P. R. Payne, P. Garcia, P. Eisenberger, J. C. H. Yim, L. L. Schafer, Org. Lett. 2013, 15, 2182.
- [5] The regioselective formation of the less substituted imine from an α substituted 2° alicyclic amine has for instance been achieved by the carefully controlled deprotonation of *N*-Cl prolinol derivatives and

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related species. Examples: a) B. A. Horenstein, R. F. Zabinski, V. L. Schramm, *Tetrahedron Lett.* **1993**, *34*, 7213; b) R. H. Furneaux, G. Limberg, P. C. Tyler, V. L. Schramm, *Tetrahedron* **1997**, *53*, 2915; c) B. G. Davis, M. A. T. Maughan, T. M. Chapman, R. Villard, S. Courtney, Org. Lett. **2002**, *4*, 103; d) M. A. T. Maughan, I. G. Davies, T. D. W.

Claridge, S. Courtney, P. Hay, B. G. Davis, *Angew. Chem. Int. Ed.* **2003**, *42*, 3788.

- [6] Examples of regioselective α'-C-H bond functionalization of protected 2° alicyclic amines with an existing α-substituent: a) N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* 2001, *123*, 10935; b) H. M. L. Davies, C. Venkataramani, T. Hansen, D. W. Hopper, *J. Am. Chem. Soc.* 2003, *125*, 6462; c) S. J. Pastine, D. V. Gribkov, D. Sames, *J. Am. Chem. Soc.* 2006, *128*, 14220; d) J. E. Spangler, Y. Kobayashi, P. Verma, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* 2015, *137*, 11876.
- [7] For an early review, see: (a) a) M. Majewski, D. M. Gleave, J. Organomet. Chem. 1994, 470, 1; Selected key contributions: b) G. Wittig, H. J. Schmidt, H. Renner, Chem. Ber. 1962, 95, 2377; c) G. Wittig, A. Hesse, Liebigs Ann. Chem. 1971, 746, 149; d) G. Wittig, A. Hesse, Liebigs Ann. Chem. 1971, 746, 174; e) G. Wittig, G. Häusler, Liebigs Ann. Chem. 1971, 746, 185.
- [8] a) W. Chen, L. Ma, A. Paul, D. Seidel, *Nat. Chem.* 2018, *10*, 165; b) A.
 Paul, D. Seidel, *J. Am. Chem. Soc.* 2019, *141*, 8778; c) W. Chen, A.
 Paul, K. A. Abboud, D. Seidel, *Nat. Chem.* 2020, *12*, 545.
- [9] Selected recent reviews on the Mannich reaction: a) B. Karimi, D. Enders, E. Jafari, Synthesis 2013, 45, 2769; b) S. Saranya, N. A. Harry, K. K. Krishnan, G. Anilkumar, Asian J. Org. Chem. 2018, 7, 613; c) D.-J. Cheng, Y.-D. Shao, ChemCatChem 2019, 11, 2575; d) R. W. Bates, W. Ko, V. Barát, Org. Biomol. Chem. 2020, 18, 810.
- [10] For a review on the use of β-keto acids in synthesis, see: S. Mao, K. Chen, G. Yan, D. Huang, *Eur. J. Org. Chem.* **2020**, *2020*, 525.
- [11] Selected reviews on decarboxylative coupling reactions: a) N. Rodriguez, L. J. Goossen, Chem. Soc. Rev. 2011, 40, 5030; b) Y. Pan, C.-H. Tan, Synthesis 2011, 2011, 2044; c) S. Nakamura, Org. Biomol. Chem. 2014, 12, 394; d) J. Xuan, Z.-G. Zhang, W.-J. Xiao, Angew. Chem. Int. Ed. 2015, 54, 15632; e) P. Liu, G. Zhang, P. Sun, Org. Biomol. Chem. 2016, 14, 10763; f) T. Patra, D. Maiti, Chem. Eur. J. 2017, 23, 7382; g) Y. Wei, P. Hu, M. Zhang, W. Su, Chem. Rev. 2017, 117, 8864; h) M. Rahman, A. Mukherjee, I. S. Kovalev, D. S. Kopchuk, G. V. Zyryanov, M. V. Tsurkan, A. Majee, B. C. Ranu, V. N. Charushin, O. N. Chupakhin, S. Santra, Adv. Synth. Catal. 2019, 361, 2161; i) K. Hyodo, S. Nakamura, Org. Biomol. Chem. 2020, 18, 2781; j) L. McMurray, T. M. McGuire, R. L. Howells, Synthesis 2020, 52, 1719.
- [12] Examples of decarboxylative Mannich reactions of acyclic and nonenolizable cyclic imines: a) E. E. van Tamelen, J. S. Baran, *J. Am. Chem. Soc.* **1955**, 77, 4944; b) A. Ricci, D. Pettersen, L. Bernardi, F. Fini, M. Fochi, R. P. Herrera, V. Sgarzani, *Adv. Synth. Catal.* **2007**, 349, 1037; c) L. Yin, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 9610; d) J. Baudoux, P. Lefebvre, R. Legay, M.-C. Lasne, J. Rouden, *Green Chem.* **2010**, *12*, 252; e) S. Abrecht, J.-M. Adam, U. Bromberger,

R. Diodone, A. Fettes, R. Fischer, V. Goeckel, S. Hildbrand, G. Moine,
M. Weber, Org. Process Res. Dev. 2011, 15, 503; f) Y. Pan, C. W. Kee,
Z. Jiang, T. Ma, Y. Zhao, Y. Yang, H. Xue, C.-H. Tan, Chem. Eur. J.
2011, 17, 8363; g) C. Jiang, F. Zhong, Y. Lu, Beilstein J. Org. Chem.
2012, 8, 1279; h) C.-F. Yang, C. Shen, J.-Y. Wang, S.-K. Tian, Org.
Lett. 2012, 14, 3092; i) L. Yin, M. Kanai, M. Shibasaki, Tetrahedron
2012, 68, 3497; j) M. Böhm, K. Proksch, R. Mahrwald, Eur. J. Org.
Chem. 2013, 2013, 1046; k) P. Qian, Y. Dai, H. Mei, V. A. Soloshonok,
J. Han, Y. Pan, RSC Adv. 2015, 5, 26811; l) A. Lahosa, M. Yus, F.
Foubelo, J. Org. Chem. 2019, 84, 7331; m) Y. Zhang, J.-K. Li, F.-G.
Zhang, J.-A. Ma, J. Org. Chem. 2020, 85, 5580; n) H. Zhang, C. Jiang,
J.-P. Tan, H.-L. Hu, Y. Chen, X. Ren, H.-S. Zhang, T. Wang, ACS Catal.
2020, 5698.

- [13] Examples of decarboxylative Mannich reactions of enolizable cyclic imines: a) E. Anet, G. K. Hughes, E. Ritchie, *Nature* **1949**, *164*, 501; b)
 C. Schöpf, G. Benz, F. Braun, H. Hinkel, R. Rokohl, *Angew. Chem.* **1953**, *65*, 161; c) E. E. van Tamelen, J. S. Baran, *J. Am. Chem. Soc.* **1956**, *78*, 2913; d) J. Quick, R. Oterson, *Synthesis* **1976**, *1976*, 745; e)
 H. Fukawa, Y. Terao, K. Achiwa, M. Sekiya, *Chem. Lett.* **1982**, *11*, 231; f) R. K. Zaidan, P. Evans, *Eur. J. Org. Chem.* **2019**, *2019*, 5354.
- [14] Examples of Mannich reactions of enolizable cyclic imines: a) M. R. Monaco, P. Renzi, D. M. Scarpino Schietroma, M. Bella, *Org. Lett.* **2011**, *13*, 4546; b) S. Virk, S. V. Pansare, *Org. Lett.* **2019**, *21*, 5524.
- [15] For the use of nitrones in decarboxylative Mannich reactions, see: V. G. Lisnyak, T. Lynch-Colameta, S. A. Snyder, *Angew. Chem. Int. Ed.* 2018, 57, 15162.
- [16] Presumably, the free β -keto acid is required in the alkylation step, with the corresponding lithium salt being less effective.
- Selected methods for the synthesis of polycyclic dihydroquinolones involving C–H bond functionalization: a) D.-F. Chen, Z.-Y. Han, Y.-P. He, J. Yu, L.-Z. Gong, Angew. Chem. Int. Ed. 2012, 51, 12307; b) G. Zhang, S. Wang, Y. Ma, W. Kong, R. Wang, Adv. Synth. Catal. 2013, 355, 874; c) C. Huo, M. Wu, X. Jia, H. Xie, Y. Yuan, J. Tang, J. Org. Chem. 2014, 79, 9860.
- [18] While full consumption of the amine starting materials was typically observed, a quantitative assessment of the mass balance is not yet possible. Competing imine-trimer formation cannot be ruled out at present and intractable polar byproducts are often formed. In case of α -substituted amine starting materials, small amounts of the regioisomeric imines were also observed. These species did not engage in the alkylation reaction and were readily separable from the target compounds.
- [19] a) D. Compère, C. Marazano, B. C. Das, *J. Org. Chem.* **1999**, *64*, 4528;
 b) F.-X. Felpin, J. Lebreton, *J. Org. Chem.* **2002**, *67*, 9192; c) G. Zheng,
 L. P. Dwoskin, P. A. Crooks, *J. Org. Chem.* **2004**, *69*, 8514; d) J. Ryan,
 M. Šiaučiulis, A. Gomm, B. Maciá, E. O'Reilly, V. Caprio, *J. Am. Chem.*Soc. **2016**, *138*, 15798.

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