Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

Check for updates

Cite this: *Chem. Sci.*, 2022, **13**, 99

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 25th October 2021
Accepted 25th November 2021

DOI: 10.1039/d1sc05876b

rsc.li/chemical-science

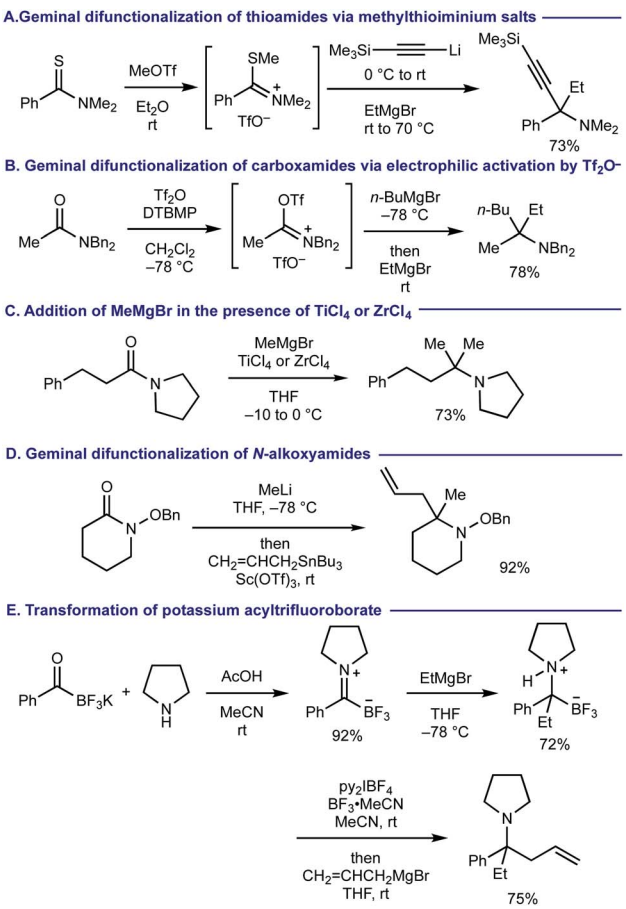
Iterative addition of carbon nucleophiles to *N,N*-dialkyl carboxamides for synthesis of α-tertiary amines†

Jiahua Chen, Jun Wei Lim, Derek Yiren Ong and Shunsuke Chiba *

A protocol for the synthesis of α-tertiary amines was developed by iterative addition of carbon nucleophiles to *N,N*-dialkyl carboxamides. Nucleophilic 1,2-addition of organolithium reagents to carboxamides forms anionic tetrahedral carbinolamine (hemiaminal) intermediates, which are subsequently treated with bromotrimethylsilane (Me_3SiBr) followed by organomagnesium (Grignard) reagents, organolithium reagents or tetrabutylammonium cyanide, affording α-tertiary amines. Employment of (trimethylsilyl) methylmagnesium bromide as the 2nd nucleophile allowed for aza-Peterson olefination of the resulting α-tertiary (trimethylsilyl)methylamines with acidic work-up, resulting in the formation of 1,1-diarylethylenes.

Introduction

α,α,α-Trisubstituted amines (α-tertiary amines) are found as core structural motifs in various biologically active natural alkaloids[1] and are identified as a key functional unit for drug discovery programs.[2] Although the sterically hindered nature of α-tertiary amines has rendered their synthetic approaches more challenging, significant advancements of their synthesis have recently been made.[3–6] Among them, geminal difunctionalization on carbonyl oxygen of readily accessible and bench-stable carboxamides *via* deoxygenative installation of two carbon–carbon bonds has been considered as one of the most practical routes to α-tertiary amines.[7,8] However, this approach generally necessitates pre-conversion of carboxamides to methylthioiminium salts *via* thiocarboxamides (Scheme 1A)[9] or trifluoromethanesulfonyloxyiminium salts (Scheme 1B),[10] prior to adding two fold organomagnesium or organolithium reagents. There are several exceptions that enable the direct use of carboxamides without their preactivation for the geminal difunctionalization. For example, dimethylation of carboxamides with methylmagnesium bromide (MeMgBr) could be performed by the stoichiometric use of oxophilic Lewis acids such as $TiCl_4$ and $ZrCl_4$, whereas carbanion reagents other than MeMgBr were not examined (Scheme 1C).[11] The use of *N*-alkoxyamides allowed for iterative installation of two carbon nucleophiles, where the 2nd carbon nucleophile should be added in the



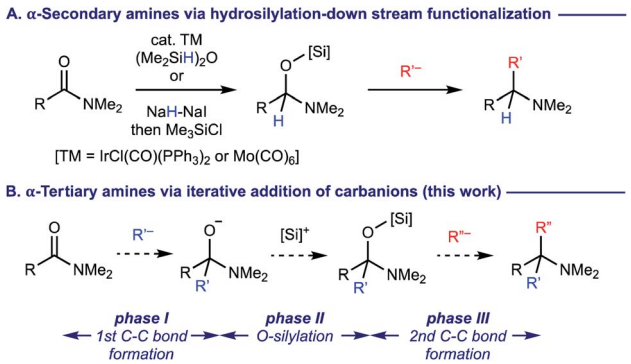
Scheme 1 Prior arts on the synthesis of α-tertiary amines *via* geminal difunctionalization of carbonyl groups.

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore. E-mail: shunsuke@ntu.edu.sg

† Electronic supplementary information (ESI) available: Experimental details, including procedures, syntheses and characterization of new compounds; ^1H and ^{13}C NMR spectra. CCDC 2105303. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc05876b

This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

(cc) BY-NC



Scheme 2 Geminal difunctionalization of carbonyl groups *via* *O*-silylated hemiaminal intermediates.

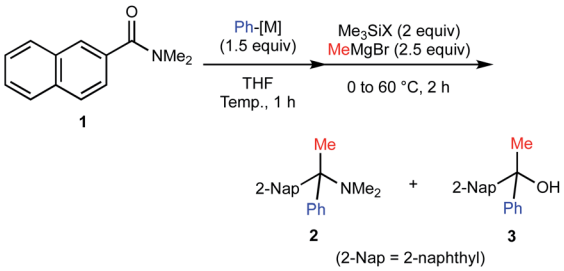
presence of acid additives (Scheme 1D).[12] A sequential transformation of potassium acyltrifluoroborates has recently been developed for the synthesis of α-tertiary amines *via* the geminal difunctionalization on carbonyl oxygen *via* (i) conversion of acyltrifluoroborates to acyltrifluoroborate-iminiums by treatment with *N*,*N*-dialkylamines; (ii) addition of Grignard reagents (the 1st carbanion) to form α-aminoalkyltrifluoroborates; (iii) oxidation with bis(pyridine)iodonium(I) tetrafluoroborate (py_2IBF_4) to iminium ions followed by addition of Grignard reagents (the 2nd carbanion) (Scheme 1E).[13] Nonetheless, synthesis of α-tertiary amines *via* the iterative installation of two different carbon substituents to carboxamides without their prefunctionalization remains an unmet challenge.

To develop a more concise and straightforward route to α-tertiary amines from carboxamides, we wondered if anionic tetrahedral carbinolamine (hemiaminal) intermediates formed upon addition of the 1st carbanion reagents[14] could successively incorporate the 2nd carbanion reagents *via* deoxygenation. Building on the recent precedents on the successful functionalization of *O*-silylated hemiaminal intermediates, which are generated *via* transition-metal catalyzed hydrosilylation[15] or controlled hydride reduction followed by silylation[16] with carbon nucleophiles such as Grignard reagents to form α-secondary amines (Scheme 2A), we surmised that the synthesis of α-tertiary amines from carboxamides might be realized by the silylation of anionic hemiaminal intermediates upon addition of the 1st carbanion nucleophiles and the ensuing engagement of the 2nd carbanion reagents (Scheme 2B). The essential keys to enable this proposed process are (i) a proper choice of the 1st carbon nucleophiles for the smooth construction of anionic hemiaminal intermediates with prevention of their decomposition before the engagement of the 2nd nucleophiles (phase I); (ii) an efficient *O*-silylation of sterically hindered anionic hemiaminal intermediates (phase II) followed by the 2nd C–C bond formation (phase III).[17] We describe our findings herein.

Results and discussion

We embarked on our investigation for the geminal functionalization of *N*,*N*-dimethyl-2-naphthamide (**1**) *via* phenylation and methylation (Table 1). We observed that addition of pre-

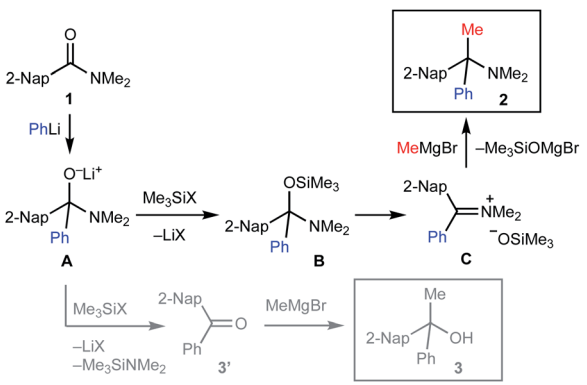
Table 1 Optimization of the reaction conditions[a]



Entry	**1** (mmol)	Ph-[M]	Temp [°C]	Me_3SiX	Yield[c] [%] **2**	**3**
1	0.5	PhLi[b]	−78 to 0	Me_3SiCl	68	25
2	0.5	PhLi[b]	−78 to 0	Me_3SiBr	89 (84)	8
3	15	PhLi[b]	−78 to 0	Me_3SiBr	90 (86)	10
4	0.5	PhLi[c]	−78 to 0	Me_3SiBr	70	5
5	0.5	PhMgBr[d]	0 to 60	Me_3SiBr	0	13[e]

[a] ^{1}H NMR yields based on the internal standard. The isolated yield is in parentheses. [b] PhLi was pre-prepared from PhBr and Li in Et_2O and titrated before use. [c] PhLi was generated *in situ* from PhBr (0.75 mmol) and *tert*-BuLi (1.5 mmol, 1.32 M in pentane) in THF, and directly used for the reaction with **1**. [d] PhMgBr was pre-prepared from PhBr and Mg in THF and titrated before use. [e] 2-Naphthyl phenyl ketone (**3′**) was formed in 52% yield.

prepared and titrated phenyllithium (PhLi) proceeded smoothly and subsequent treatment with chlorotrimethylsilane (Me_3SiCl) and methylmagnesium bromide (MeMgBr) at 60 °C afforded desired α-tertiary amine **2** in 68% yield along with the formation of α-tertiary alcohol **3** in 25% yield (entry 1). We found that the use of bromotrimethylsilane (Me_3SiBr) could improve the yield of α-tertiary amine **2** to 89% (84% isolated) yield (entry 2). This protocol was found to be scalable up to 15 mmol scale without detrimental impact on the yield of **2** (entry 3). The use of PhLi prepared *in situ via* halogen–lithium exchange using bromobenzene and *tert*-butyllithium afforded amine **2** in 70% yield (entry 4). Despite slightly diminished efficiency, this approach circumvents pre-preparation of



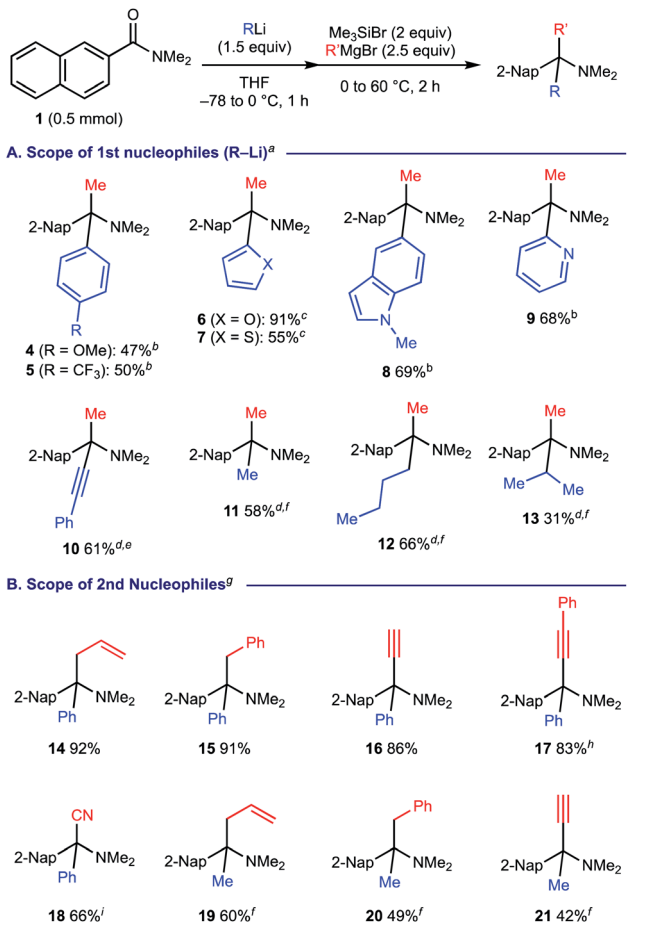
Scheme 3 Proposed reaction pathways.

© 2022 The Author(s). Published by the Royal Society of Chemistry

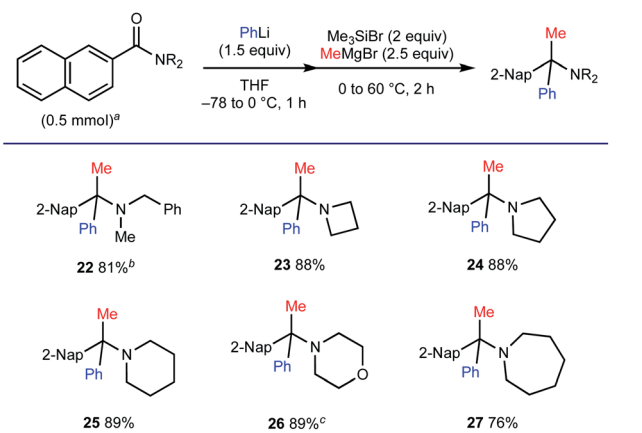
organolithium reagents (*vide infra*). However, the reaction with phenylmagnesium bromide (PhMgBr) as the 1st carbanion did not afford desired amine **2** at all (entry 5). In this case, formation of alcohol **3** was observed in 13% yield along with 2-naphthyl phenyl ketone (**3′**) in 52% yield, indicating insufficient *O*-silylation of the corresponding anionic carbinol amine intermediate generated from 2-naphthamide **1** and PhMgBr.

The proposed mechanism of the geminal difunctionalization of 2-naphthamide **1** is depicted in Scheme 3. Addition of PhLi to the amide carbonyl group forms anionic hemiaminal intermediate **A**, which could be detected as a stable form even at ambient temperature by ^{1}H and ^{13}C NMR analyses (see the ESI†). *O*-Silylation of **A** with halotrimethylsilane (Me_3SiX) resulted in the formation of **B** and ensuing addition of MeMgBr results in the formation of amine **2** *via* iminium ion intermediate **C**. On the other hand, electrophilic activation of the amino group of **A** by Me_3SiX collapses **A** into ketone **3′**, which is trapped with MeMgBr to provide alcohol **3**. We speculated that the use of more electrophilic Me_3SiBr renders the reaction course more selective toward the formation of iminium **C** *via* efficient *O*-silylation of **A** over that of ketone **D** *via* *N*-silylation.

We next investigated the scope of the reaction with respect to the carbanion reagents using 2-naphthamide **1** (Scheme 4). As for the organolithium reagents as the 1st carbanion, the method was found to be compatible with the use of both electron-rich and electron-deficient aryllithium as well as 2-thienyllithium, 2-furyllithium, 5-indolyllithium and 2-pyridyllithium, providing the corresponding amines **4–9** in good to moderate yields (Scheme 4A). The protocol is amenable to use lithium phenylacetylide to form propargylamine **10**. As for alkyllithium reagents, the present protocol could employ methyllithium and butyllithium, efficiently providing the corresponding α-tertiary amines **11** and **12**, while the use of isopropyllithium resulted in moderate efficiency for the formation of amine **13** (31% yield). We then examined the compatibility of the 2nd carbanion reagents using PhLi or MeLi as the 1st carbanion reagent (Scheme 4B). With PhLi as the 1st carbanion, the method was amenable to engage allyl and benzyl Grignard reagents (for **14** and **15**). Installation of acetylenic moieties could also be implemented with good efficiency using ethynylmagnesium bromide and lithium phenylacetylide, respectively (for **16** and **17**). We found that the use of tetrabutylammonium cyanide



Scheme 4 Scope with respect to the nucleophiles. [a]The reactions conditions: 2-naphthamide **1** (0.5 mmol), 1st organolithium reagent (1.5 equiv.) at −78 to 0 °C for 1 h, followed by Me_3SiBr (2 equiv.) and MeMgBr (2.5 equiv.) at 0 °C, then stirring at 60 °C for 2 h. Isolated yields were recorded. [b]Aryllithium was prepared by the treatment of the corresponding aryl bromide (0.75 mmol) with *t*-BuLi (1.5 mmol) in THF at −78 °C. [c]2-Furanyl- or 2-thienyllithium was prepared by the treatment of furan or thiophene (0.75 mmol) with BuLi (0.75 mmol) in THF at −78 to 0 °C. [d]The commercially available organolithium reagents were used after titration. [e]Lithium phenylacetylide (3 equiv.) at 60 °C for 2 h, followed by Me_3SiBr (2 equiv.) and MeMgBr (3 equiv.) at 0 °C, then stirring at 60 °C for 2 h. [f]MeMgBr (3 equiv.) was used. [g]The reaction conditions: carboxamide **1** (0.5 mmol), PhLi or MeLi (1.5 equiv.) at −78 to 0 °C for 1 h, followed by Me_3SiBr (2 equiv.) and organomagnesium reagents (2.5 equiv.) as the 2nd nucleophile (2.5 equiv.) at 0 °C, then stirring at 60 °C for 2 h. Isolated yields were recorded. [h]Lithium phenylacetylide was used as the 2nd nucleophile. [i]Bu_4NCN was used as the 2nd nucleophile.



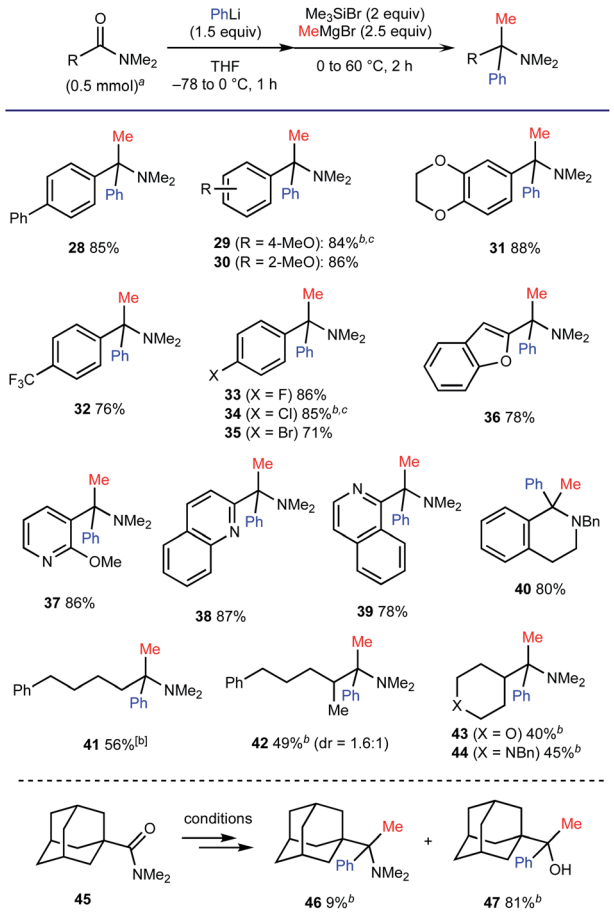
Scheme 5 Substituent compatibility of amide nitrogen. [a]The reactions conditions: carboxamides (0.5 mmol), PhLi (1.5 equiv.) at −78 to 0 °C for 1 h, followed by Me_3SiBr (2 equiv.) and MeMgBr (2.5 equiv.) at 0 °C, then stirring at 60 °C for 2 h. Isolated yields were recorded. [b]After addition of Me_3SiBr at 0 °C, the mixture was stirred at room temperature for 0.5 h before the mixture was treated with MeMgBr at 0 °C and heated at 60 °C for 2 h. [c]After addition of Me_3SiBr at 0 °C, the mixture was stirred at 60 °C for 1 h before the mixture was treated with MeMgBr at 0 °C and heated at 60 °C for 2 h.

© 2022 The Author(s). Published by the Royal Society of Chemistry

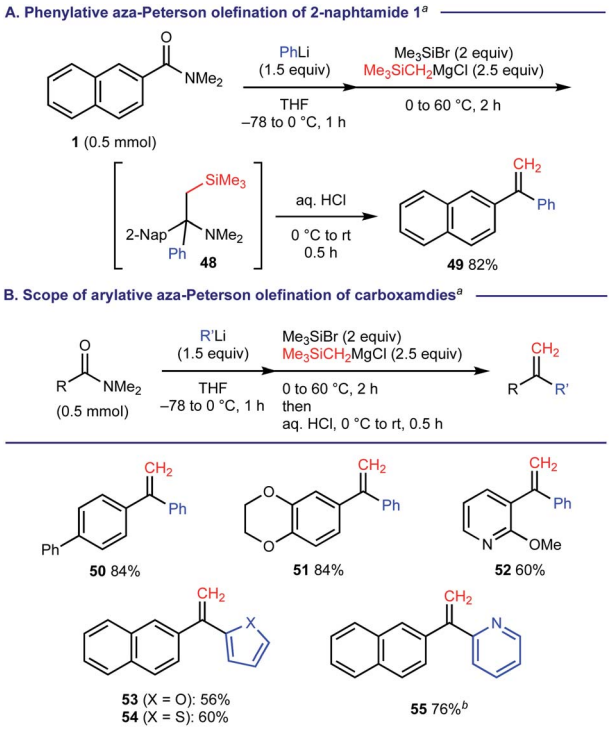
enables the downstream Strecker reaction to form α-cyano amine **18** in good yield. With MeLi as the 1st carbanion, similarly, the protocol was compatible to incorporate allyl, benzyl, and alkynyl motifs in the corresponding α-tertiary amines **19–21**.[18]

Substituent compatibility of amide nitrogen was investigated next (Scheme 5). This method allowed for the synthesis of α-tertiary amines starting from *N*-benzyl-*N*-methylamide (for **22**) and those based on azetidine, pyrrolidine, piperidine, morpholine and azepane (for **23–27**).

We also examined the compatibility of various carboxamides, using a combination of PhLi and MeMgBr for the geminal difunctionalization (Scheme 6). As for aromatic amides, the process tolerated substituents with different electronic properties such as a biphenyl moiety (for **28**), electron-donating groups (for **29–31**) and electron-withdrawing groups including a trifluoromethyl group (for **32**) and halogen atoms (for **33–35**). Carboxamides based on electron-rich benzofuran (for **36**) as well as electron-deficient 6-membered rings including pyridine, quinoline, and isoquinoline moieties (for **37–39**) were also compatible. The ability for concise synthesis of 1,1-disubstituted tetrahydroisoquinoline **40** (ref. 19) from the corresponding lactam is also one of the advantageous features of the method. The present protocol also allowed for the geminal difunctionalization of aliphatic amides. The reactions of α-primary and α-secondary alkyl carboxamides having enolizable α-protons proceeded to afford the corresponding amines **41–44** in good to moderate yields. However, the reaction of sterically congested 1-adamantyl carboxamide **45** resulted in the formation of alcohol **47** as the major product.



Scheme 6 Scope with respect to the carboxamides. [a]The reactions conditions: carboxamides (0.5 mmol), PhLi (1.5 equiv.) at −78 to 0 °C for 1 h, followed by Me_3SiBr (2 equiv.) and MeMgBr (2.5 equiv.) at 0 °C, then stirring at 60 °C for 2 h. Isolated yields were recorded. [b]3 equiv. of MeMgBr was used. [c]After addition of MeMgBr, the reaction mixture was stirred at 60 °C for 3 h. Bn = benzyl.



Scheme 7 Arylative aza-Peterson olefination of carboxamides. [a]The reactions conditions: carboxamides (0.5 mmol), PhLi (1.5 equiv.) at −78 to 0 °C for 1 h, followed by Me_3SiBr (2 equiv.) and Me_3SiCH_2MgCl (2.5 equiv.) at 0 °C, then stirring at 60 °C for 2 h; water (1 mL) at 0 °C, and then 3 M HCl aqueous solution (5 mL), stirring at room temperature for 0.5 h. Isolated yields were recorded. [b]After addition of 6 M HCl aqueous solution, the mixture was stirred at 60 °C for 2 h.

When (trimethylsilyl)methylmagnesium chloride was used as the 2nd carbanion reagent upon treatment of 2-naphthamide **1** with PhLi, we observed that the resulting α-tertiary amine **48** was further converted into 1,1-diarylethylene **49** upon the aqueous acid work-up *via* elimination of silylamine (Scheme 7A). This process could be regarded as phenylative aza-Peterson olefination[20] of carboxamide **1** and we found that this protocol is applicable for the facile construction of unsymmetrical 1,1-diarylethylenes **50–55** (Scheme 7B).

Conclusions

In summary, we have developed a transition-metal free protocol for the synthesis of α-tertiary amines by iterative addition of

© 2022 The Author(s). Published by the Royal Society of Chemistry

carbon nucleophiles to readily available and bench stable *N*,*N*-dialkyl carboxamides. Given the broad scope and operationally simple protocol of the method, we view it to be adaptable in various synthetic endeavours.

Data availability

All synthetic procedures, characterization data, spectroscopic data, supplementary schemes, figures and tables, and detailed crystallographic information are provided in the ESI.†

Author contributions

S. C. conceived the project and designed the studies. J. C., J. W. L. and D. Y. O. carried out the experiments. All the authors discussed the results and contributed to the preparation of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by funding from the Nanyang Technological University (NTU) and the Singapore Ministry of Education (Academic Research Fund Tier 2: MOE2019-T2-1-089) (for S. C.).

Notes and references

1 A. Hager, N. Vrielink, D. Hager, J. Lefranc and D. Trauner, *Nat. Prod. Rep.*, 2016, **33**, 491–522.

2 K. R. Campos, P. J. Coleman, J. C. Alvarez, S. D. Dreher, R. M. Garbaccio, N. K. Terrett, R. D. Tillyer, M. D. Truppo and E. R. Parmee, *Science*, 2019, **363**, eaat0805.

3 For selected reviews, see: (*a*) A. Trowbridge, S. M. Walton and M. J. Gaunt, *Chem. Rev.*, 2020, **120**, 2613–2692; (*b*) M. S. M. Pearson-Long, F. Boeda and P. Bertus, *Adv. Synth. Catal.*, 2017, **359**, 179–201; (*c*) H. Jiang and A. Studer, *Chem. Soc. Rev.*, 2020, **49**, 1790–1811; (*d*) J. Clayden, M. Donnard, J. Lefranc and D. J. Tetlow, *Chem. Commun.*, 2011, **47**, 4624–4639.

4 For addition of carbon nucleophiles to *N*-substituted ketimines, see: (*a*) T. Kano, Y. Aota and K. Maruoka, *Angew. Chem., Int. Ed.*, 2017, **56**, 16293–16296; (*b*) L. Yin, Y. Otsuka, H. Takada, S. Mouri, R. Yazaki, N. Kumagai and M. Shibasaki, *Org. Lett.*, 2013, **15**, 698–701; (*c*) C. J. Pierce, M. Nguyen and C. H. Larsen, *Angew. Chem., Int. Ed.*, 2012, **51**, 12289–12292; (*d*) M. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600–3740; (*e*) R. Wada, T. Shibuguchi, S. Makino, K. Oisaki, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 7687–7691; (*f*) D. A. Cogan and J. A. Ellman, *J. Am. Chem. Soc.*, 1999, **121**, 268–269.

5 For C–H amination, see: (*a*) K. Kiyokawa, T. Watanabe, L. Fra, T. Kojima and S. Minakata, *J. Org. Chem.*, 2017, **82**, 11711–11720; (*b*) J. L. Roizen, D. N. Zalatan and J. Du Bois, *Angew. Chem., Int. Ed.*, 2013, **52**, 11343–11346; (*c*) Q. Michaudel, D. Thevenet and P. S. Baran, *J. Am. Chem. Soc.*, 2012, **134**, 2547–2550.

6 For C–H alkylation/arylation of amines *via* photoredox catalysis, see: (*a*) M. C. Nicastri, D. Lehnherr, Y.-h. Lam, D. A. DiRocco and T. Rovis, *J. Am. Chem. Soc.*, 2020, **142**, 987–998; (*b*) D. Lehnherr, Y.-h. Lam, M. C. Nicastri, J. Liu, J. A. Newman, E. L. Regalado, D. A. DiRocco and T. Rovis, *J. Am. Chem. Soc.*, 2020, **142**, 468–478; (*c*) 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 and A. J. Cresswell, *Angew. Chem., Int. Ed.*, 2020, **59**, 14986–14991; (*d*) M. A. Ashley, C. Yamauchi, J. C. K. Chu, S. Otsuka, H. Yorimitsu and T. Rovis, *Angew. Chem., Int. Ed.*, 2019, **58**, 4002–4006; (*e*) D. Vasu, A. L. Fuentes de Arriba, J. A. Leitch, A. de Gombert and D. J. Dixon, *Chem. Sci.*, 2019, **10**, 3401–3407; (*f*) J. Ye, I. Kalvet, F. Schoenebeck and T. Rovis, *Nat. Chem.*, 2018, **10**, 1037–1041; (*g*) J. Rong, P. H. Seeberger and K. Gilmore, *Org. Lett.*, 2018, **20**, 4081–4085.

7 D. Seebach, *Angew. Chem., Int. Ed.*, 2011, **50**, 96–101.

8 For selected reviews on functionalization of carboxamides, see: (*a*) D. Y. Ong, J.-h. Chen and S. Chiba, *Bull. Chem. Soc. Jpn.*, 2020, **93**, 1339–1349; (*b*) D. Kaiser, A. Bauer, M. Lemmerer and N. Maulide, *Chem. Soc. Rev.*, 2018, **47**, 7899–7925; (*c*) A. Chardon, E. Morisset, J. Rouden and J. Blanchet, *Synthesis*, 2018, **50**, 984–997; (*d*) T. Sato, M. Yoritate, H. Tajima and N. Chida, *Org. Biomol. Chem.*, 2018, **16**, 3864–3875; (*e*) A. Volkov, F. Tinnis, T. Slagbrand, P. Trillo and H. Adolfsson, *Chem. Soc. Rev.*, 2016, **45**, 6685–6697; (*f*) D. Kaiser and N. Maulide, *J. Org. Chem.*, 2016, **81**, 4421–4428; (*g*) V. Pace, W. Holzer and B. Olofsson, *Adv. Synth. Catal.*, 2014, **356**, 3697–3736.

9 (*a*) T. Murai and Y. Mutoh, *Chem. Lett.*, 2012, **41**, 2–8; (*b*) A. Agosti, S. Britto and P. Renaud, *Org. Lett.*, 2008, **10**, 1417–1420; (*c*) T. Murai, R. Toshio and Y. Mutoh, *Tetrahedron*, 2006, **62**, 6312–6320; (*d*) T. Murai, Y. Mutoh, Y. Ohta and M. Murakami, *J. Am. Chem. Soc.*, 2004, **126**, 5968–5969.

10 (*a*) H. Chen, Y.-H. Huang, J.-L. Ye and P.-Q. Huang, *J. Org. Chem.*, 2019, **84**, 9270–9281; (*b*) K.-J. Xiao, J.-M. Luo, X.-E. Xia, Y. Wang and P.-Q. Huang, *Chem.–Eur. J.*, 2013, **19**, 13075–13086; (*c*) H.-H. Huo, X.-E. Xia, H.-K. Zhang and P.-Q. Huang, *J. Org. Chem.*, 2013, **78**, 455–465; (*d*) G. Bélanger, G. O'Brien and R. Larouche-Gauthier, *Org. Lett.*, 2011, **13**, 4268–4271; (*e*) K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang and P.-Q. Huang, *Angew. Chem., Int. Ed.*, 2010, **49**, 3037–3040.

11 S. M. Denton and A. Wood, *Synlett*, 1999, 55–56.

12 (*a*) Y. Yanagita, H. Nakamura, K. Shirokane, Y. Kurosaki, T. Sato and N. Chida, *Chem.–Eur. J.*, 2013, **19**, 678–684; (*b*) G. Vincent, R. Guillot and C. Kouklovsky, *Angew. Chem., Int. Ed.*, 2011, **50**, 1350–1353.

13 (*a*) M. K. Jackl, A. Schuhmacher, T. Shiro and J. W. Bode, *Org. Lett.*, 2018, **20**, 4044–4047; (*b*) T. Shiro, A. Schuhmacher, M. K. Jackl and J. W. Bode, *Chem. Sci.*, 2018, **9**, 5191–5196.

© 2022 The Author(s). Published by the Royal Society of Chemistry

14 (*a*) M. Adler, S. Adler and G. Boche, *J. Phys. Org. Chem.*, 2005, **16**, 193–209; (*b*) S. Ghinato, D. Territo, A. Maranzana, V. Capriati, M. Blangetti and C. Prandi, *Chem.–Eur. J.*, 2021, **27**, 2868–2874; (*c*) J. de Jong, D. Heijnen, H. Helbert and B. L. Feringa, *Chem. Commun.*, 2019, **55**, 2908–2911; (*d*) C. Liu, M. Achtenhagen and M. Szostak, *Org. Lett.*, 2016, **18**, 2375–2378; (*e*) M. Adler, M. Marsch, N. S. Nudelman and G. Boche, *Angew. Chem., Int. Ed.*, 1999, **38**, 1261–1263; (*f*) G. A. Olah, G. K. S. Prakash and M. Arvanaghi, *Synthesis*, 1984, 228–230.

15 For selected reports, see: (*a*) D. Matheau-Raven, P. Gabriel, J. A. Leitch, Y. A. Almehmadi, K. Yamazaki and D. J. Dixon, *ACS Catal.*, 2020, **10**, 8880–8897; (*b*) P. Gabriel, A. W. Gregory and D. J. Dixon, *Org. Lett.*, 2019, **21**, 6658–6662; (*c*) Y. Takahashi, T. Sato and N. Chida, *Chem. Lett.*, 2019, **48**, 1138–1141; (*d*) L.-G. Xie and D. J. Dixon, *Nat. Commun.*, 2018, **9**, 2841; (*e*) P. Trillo, T. Slagbrand and H. Adolfsson, *Angew. Chem., Int. Ed.*, 2018, **57**, 12347–12351; (*f*) W. Ou, F. Han, X.-N. Hu, H. Chen and P.-Q. Huang, *Angew. Chem., Int. Ed.*, 2018, **57**, 11354–11358; (*g*) Á. L. Fuentes de Arriba, E. Lenci, M. Sonawane, O. Formery and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2017, **56**, 3655–3659; (*h*) L.-G. Xie and D. J. Dixon, *Chem. Sci.*, 2017, **8**, 7492–7497; (*i*) P.-Q. Huang, W. Ou and F. Han, *Chem. Commun.*, 2016, **52**, 11967–11970; (*j*) M. Nakajima, T. Sato and N. Chida, *Org. Lett.*, 2015, **17**, 1696–1699.

16 D. Y. Ong, D. Fan, D. J. Dixon and S. Chiba, *Angew. Chem., Int. Ed.*, 2020, **59**, 11903–11907.

17 The synthesis of α-secondary amines *via* two-fold addition of Grignard reagents to *N*,*N*-dialkylformamides in the presence of titanium(IV) isopropoxide [$Ti(O\text{-}iPr)_4$] and chlorotrimethylsilane (Me_3SiCl) was developed by de Meijere. However, this method is only applicable to the conversion of formamides and thus not suitable for the synthesis of α-tertiary amines, see: O. Tomashenko, V. Sokolov, A. Tomashevskiy, H. A. Buchholz, U. Welz-Biermann, V. Chaplinski and A. de Meijere, *Eur. J. Org. Chem.*, 2008, 5107–5111.

18 The method was not capable for installation of a phenyl group using PhMgBr as the 2nd carbanion reagent (see the ESI†).

19 (*a*) X. Li and I. Coldham, *J. Am. Chem. Soc.*, 2014, **136**, 5551–5554; (*b*) M. Ludwig, C. E. Hoesl, G. Höfner and K. T. Wanner, *Eur. J. Med. Chem.*, 2006, **41**, 1003–1010; (*c*) M. Ohkubo, A. Kuno, K. Katsuta, Y. Ueda, K. Shirakawa, H. Nakanishi, I. Nakanishi, T. Kinoshita and H. Takasugi, *Chem. Pharm. Bull.*, 1996, **44**, 95–102.

20 (*a*) M. Das and D. F. O'Shea, *Org. Lett.*, 2016, **18**, 336–339; (*b*) M. Das, A. Manvar, M. Jacolot, M. Blangetti, R. C. Jones and D. F. O'Shea, *Chem.–Eur. J.*, 2015, **21**, 8737–8740.

© 2022 The Author(s). Published by the Royal Society of Chemistry