



Aminoarylation of alkynes using diarylanilines†

 Zi Liu and Michael F. Greaney *

 Cite this: *Chem. Commun.*, 2024, 60, 6296

 Received 24th April 2024,
 Accepted 21st May 2024

DOI: 10.1039/d4cc01935k

rsc.li/chemcomm

Intermolecular aminoarylation of alkynes is described, via addition of diarylanilines to alkynes and Smiles–Truce rearrangement. The transformation manipulates the C–N bond of anilines directly, with no requirement for organometallic reagents or transition metal catalysis. The enaminoate products are versatile building blocks for different classes of heterocycles.

The Smiles–Truce rearrangement (STR) is a powerful approach to C–C bond formation that enables arylation under simple, sustainable conditions (Scheme 1A).¹ By exchanging an aryl C–heteroatom bond for a C–C bond, functionalised arene and hetero-arene structures can be built efficiently from simple starting materials, with no requirement for precious metal catalysis. The STR gains substantial utility if it is set up as a domino or multi-component coupling process, whereby an initial intermolecular bond formation creates the key reactive intermediate for arene transfer, which can undergo rearrangement to the desired arene in one operation. Some recent examples are shown in Scheme 1, which illustrate different domino STR design approaches in the anionic and radical regimes.²

Early work in this area was defined by the sulfonamide functional group, used as the key linkage in the vast majority of domino STR reactions.³ Sulfonamides are easy to prepare, enable versatile aminoarylations in both anionic and radical reaction regimes, and drive the actual rearrangement through irreversible loss of SO₂. The weak nucleophilicity of sulfonamides, however, can be problematic for domino reactions that rely on C–N bond formation as the first step. Recent work from the Stephenson and Nevado groups, for example, showed that stereogenic sulfinamides were superior to their sulfonamide analogs for radical alkene aminoarylation.⁴ Domino STR

processes have also been described for sulfones,^{2a,k,p,ab} amides,^{2w} ureas,^{2e} and sulfonates.^{2z,ac} The exploration of alternative STR linkages is in general a productive direction to develop new classes of aryating agents.

We have recently reported that dialkylanilines can undergo domino STR with the reactive intermediate benzyne, to form aminobiaryl compounds **13** (Scheme 1B).⁵ The reaction enables anilines to be used as aryating agents at the site of the C–N bond, a difficult manipulation outside of high energy diazonium chemistry, with few methods available.⁶ We were interested in developing this reaction for general alkyne aminoarylation, through reaction with ground state alkynes. Alkyne aminoarylation is a potentially high value transformation, affording versatile enamine products (**17**), but is restricted by a paucity of viable synthetic methods. Very few examples have been reported in the intermolecular mode: Lu described enamide synthesis using Rh catalysis and *N*-phenoxyacetamides, and Li has reported the Cu-catalysed addition of NFSI derivatives to make enesulfonamides. The Dong laboratory used Pd catalysis for *in situ* aminoarylation with amines and aryl halides, affording α -arylketones on work-up.⁷ Work from our laboratory described a STR approach using metal-free addition of arylsulfonamides to make enaminoates.⁸ New methods for alkyne aminoarylation are thus required, particularly ones that exploit readily available starting materials (*e.g.* **14** and **15**).

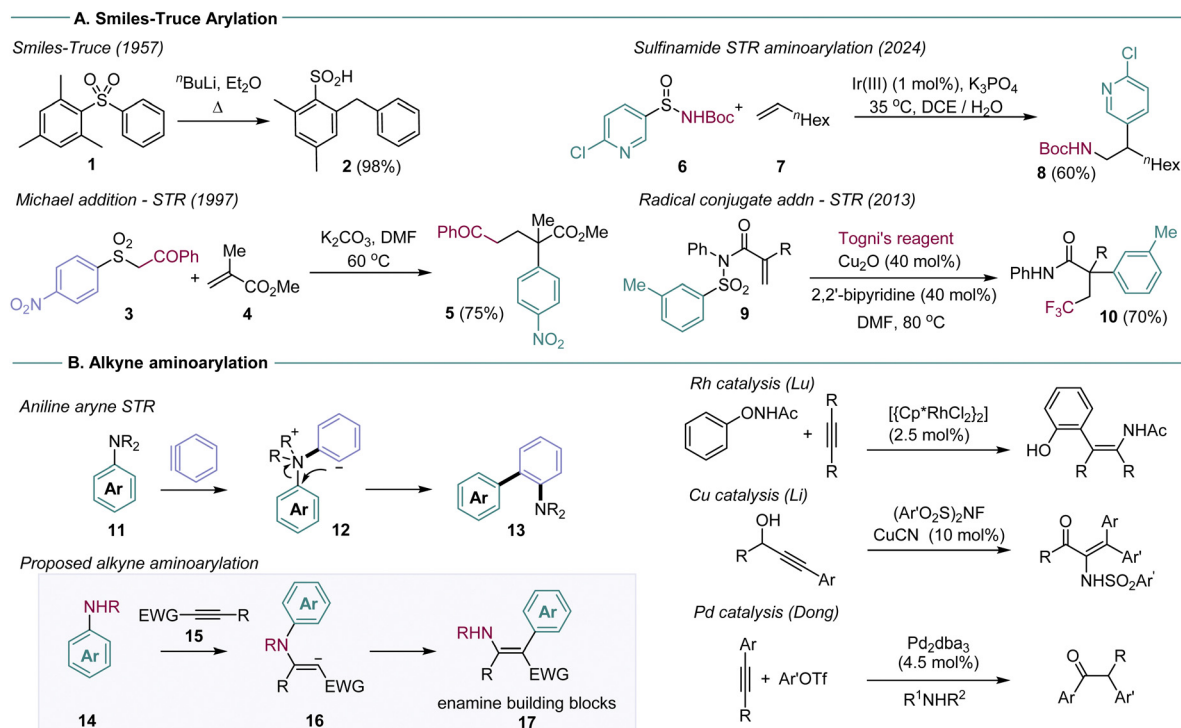
A challenge in the planned aminoarylation concerns the four-membered transition state intrinsic to the aniline STR. In our previous aryne system, the exceptional reactivity of benzyne enables capture by tertiary anilines and a subsequent charge-quenching STR from intermediate **12** (Scheme 1B). This substrate design is unlikely to work for ground state alkynes, which are typically unreactive with electron-poor tertiary anilines. We were encouraged, however, by reports of domino sulfonamide S_N2/STRs through four-membered transition states, providing some precedent for the idea.⁹ We set out to investigate secondary anilines that would be nucleophilic enough to undergo conjugate alkyne addition, but containing an electrophilic arene ring that could support the intramolecular S_NAr character of the STR.

Dept of Chemistry, University of Manchester, Oxford Rd, Manchester M13 9PL, UK.

E-mail: michael.greaney@manchester.ac.uk

† Electronic supplementary information (ESI) available: All preparative procedures, characterisation data, and NMR spectra. CCDC 2342281. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4cc01935k>





Scheme 1 (A). The Smiles–Truce rearrangement (STR) and domino examples. (B) Proposed aminoarylation.

We initially screened a series of secondary *N*-alkyl anilines with propargylate substrates, and did not observe any reactivity. Moving to diarylanilines, however, did result in a successful STR with *N,N*-(4-nitrophenyl)phenylaniline (**14a**) reacting with ethyl pent-2-ynoate (**15a**) in low conversion. Under conditions of mild base, Cs₂CO₃, in MeCN at 70 °C we isolated the aminoarylated product **17a** as the *Z*-isomer in 14% (Table 1, entry 1). X-Ray analysis confirmed the *Z*-geometry,¹⁰ in line with the selectivity we have previously observed with sulfonamide nucleophiles.⁸ The resonance-assisted H-bond¹¹ ($\delta_{\text{H}} = 11.3$ ppm) present in the

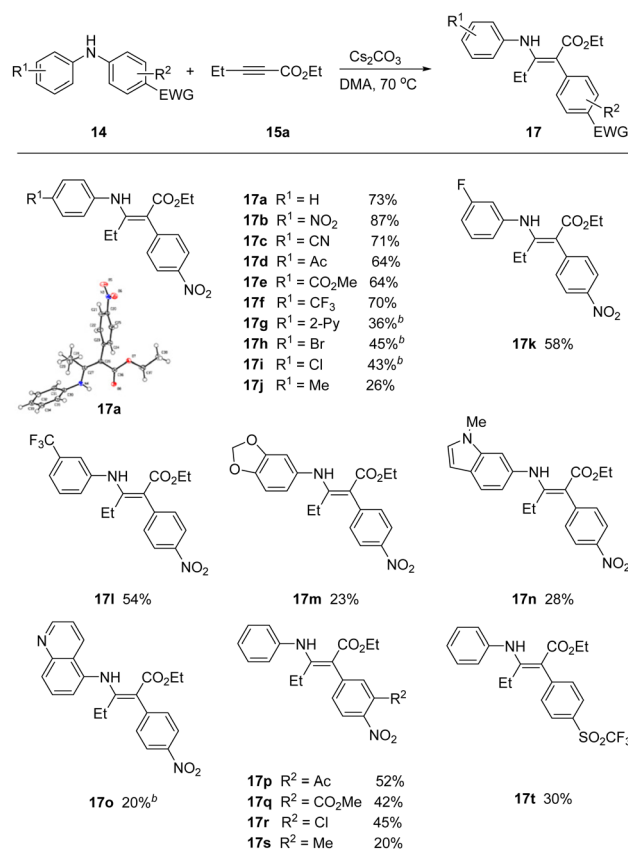
Scheme 2 Scope of anilines. ^a **14** (1.2 equiv.), **15a** (1.0 equiv.) and Cs₂CO₃ (1.5 equiv.) in DMA at 70 °C; ^b using KOH as base.

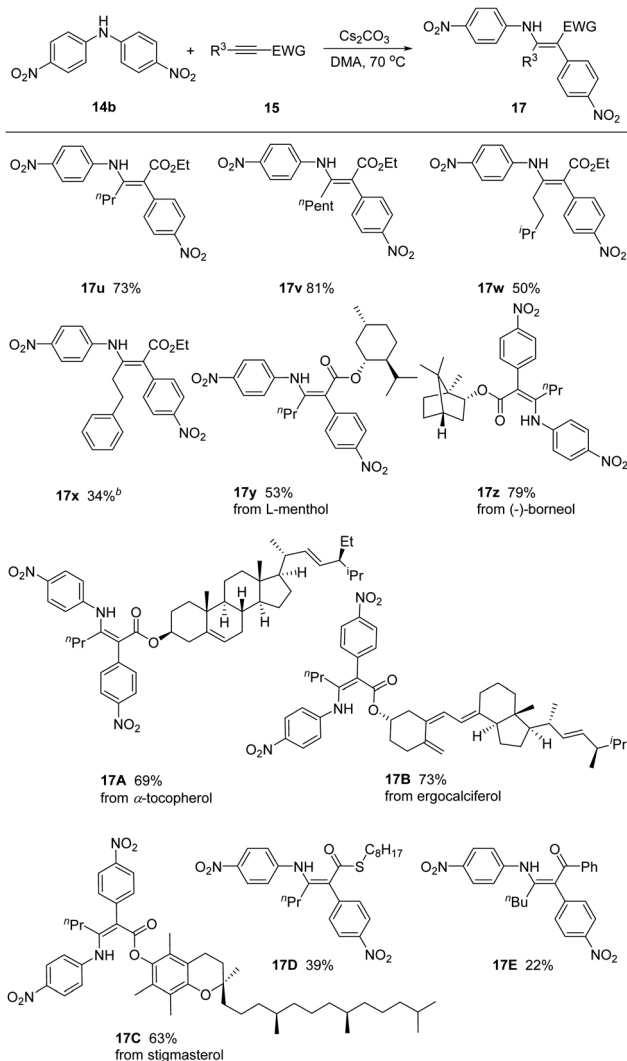
Table 1 Reaction optimisation



Entry	Base	Ratio (14a : 15a : base)	Solvent	T (°C)	Yield (%)
1	Cs ₂ CO ₃	1.2 : 1.0 : 1.5	MeCN	70	14
2	Cs ₂ CO ₃	1.2 : 1.0 : 1.5	DMSO	70	19
3	Cs ₂ CO ₃	1.2 : 1.0 : 1.5	DMA	70	56
4	Cs ₂ CO ₃	1.2 : 1.0 : 1.5	DMA	90	24
5	Cs ₂ CO ₃	1.2 : 1.0 : 1.5	DMA	50	19
6	Cs ₂ CO ₃	1.5 : 1.0 : 1.5	DMA	70	11
7	Cs ₂ CO ₃	1.0 : 1.0 : 1.5	DMA	70	18
8	Cs ₂ CO ₃	1.0 : 1.2 : 1.5	DMA	70	27
9	K ₂ CO ₃	1.2 : 1.0 : 1.5	DMA	70	ND
10	KOH	1.2 : 1.0 : 1.5	DMA	70	34
11	^t BuOK	1.2 : 1.0 : 1.5	DMA	70	19
12	NaH	1.2 : 1.0 : 1.5	DMA	70	13
13 ^a	Cs ₂ CO ₃	1.2 : 1.0 : 1.5	DMA	70	73

^a The reaction was performed under N₂.

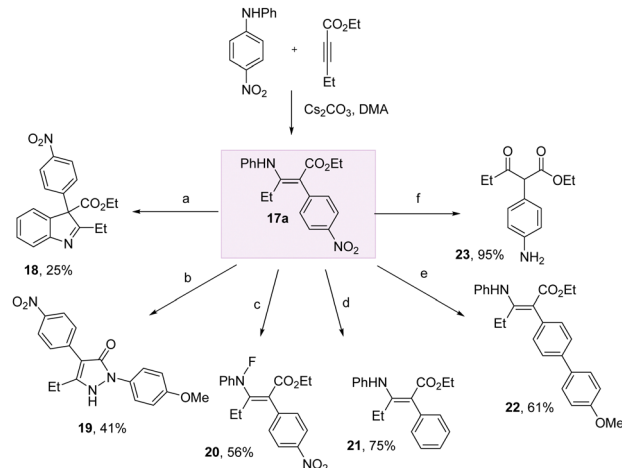




Scheme 3 Scope of alkynes. ^a **14b** (1.2 equiv.), **15** (1.0 equiv.) and Cs_2CO_3 (1.5 equiv.) in DMA at 70°C .

Z, but not the E, geometrical isomer likely drives isomerisation *in situ*.¹² A solvent screen established DMA as a better solvent choice delivering **17a** in 56% yield (Table 1, entry 3). Further modifications to temperature, stoichiometry and base choice did not advance reaction efficiency, with stronger bases in particular being poor for the reaction. We were pleased to find that conducting the reaction under inert atmosphere supplied the corresponding product **17a** in 73% overall yield (Table 1, entry 13).

With optimal conditions in hand, we screened a variety of differentially substituted diarylanilines reacting with **15a** (Scheme 2). A broad range of electron-deficient or electron-rich substituents on the phenyl ring at different positions (*meta*- or *para*-) were all tolerated under the mild reaction conditions, furnishing the corresponding rearrangement products **17** with yields up to 87%. Substrates encompassing strongly electron-withdrawing groups (**17b–17g**), including nitro, nitrile, acetyl, ester, trifluoromethyl and pyridyl, could be successfully incorporated in this process.



Scheme 4 Enaminoate transformations. ^a I_2 , K_2CO_3 , DMF, 100°C , 1 h; ^b 4-methoxyphenylhydrazine hydrochloride, EtOH, reflux, 16 h; ^c selectfluor, DCM/ H_2O , r.t., 4 days; ^d $\text{Pd}(\text{acac})_2$, Brettphos, K_3PO_4 , i PrOH, 1,4-dioxane, 130°C , overnight; ^e $\text{Pd}(\text{acac})_2$, Brettphos, K_3PO_4 , 18-crown-6, (4-methoxyphenyl)boronic acid, 1,4-dioxane, 130°C , 16 h; ^f Fe, NH_4Cl , EtOH/ H_2O , 60°C , 12 h.

The rearrangement products **17h**, **17i** and **17r** with halogen groups, providing the opportunity for further functionalization, were obtained in moderate yields 43%, 45% and 45%, respectively. More electron rich arenes were viable, but in reduced yields. For example, tolyl and the piperonyl, indolyl, and isoquinoyl heteroaryl anilines all participated, but in attenuated yields. The migratory aryl group required at least one strong electron withdrawing group, but additional substituents could be installed in the flanking position (**17p–17s**). We were able to successfully migrate the trifluoromethanesulfonyl derivative (**17t**), in place of the activating nitro group.

We next inspected the generality of alkyne substrates by employing bis(4-nitrophenyl)amine **14b** as model substrate (Scheme 3). Different alkyl substituted alkynyl ester derivatives reacted smoothly, giving the corresponding products **17u–17x** in 34–81% yields. We could link the common biologically relevant molecules L-menthol, (-)-borneol, α -tocopherol, ergocalciferol, and stigmasterol through the ester moiety, incorporating these moieties into the enaminato products **17y–17C**. Alkynes bearing different electron-withdrawing groups, such as thioester and ketone, were also feasible in this reaction, affording products **17D** and **17E** in reduced yields of 39% and 22%.

To demonstrate the practicality of this method for harnessing aniline arylation, we conducted a series of transformations on the enaminato **17a** (Scheme 4). We could access indoline and pyrazolone heterocycles **18** and **19** through treatment with iodine, and *p*-methoxyphenylhydrazine hydrochloride, respectively.

Fluorination of the N–H bond of **17a** with selectfluor in DCM/ H_2O successfully delivered **20** in 56% yield. The nitro group could be removed entirely to give the phenyl derivative **21** using Nakao's reductive palladium method. Likewise, a nitro-Suzuki was successful to give the biaryl **22** in 61% yield. The electron-poor nitroarene could be easily transformed into the electron rich aniline using Fe/ NH_4Cl in EtOH/ H_2O at 60°C ,



with concomitant hydrolysis of the enamine to give the keto-ester **23**.

In conclusion, we have developed an intermolecular aminoarylation of alkynes using anilines. The reaction allows cheap aniline building blocks to be used as arylating agents for a range of enamine syntheses, with the products directed to diverse heterocyclic products. Further applications of this process are underway in our laboratory.

We thank the Leverhulme Trust for funding (LT RPG-2021-281). Dr Avantika Hasija (University of Manchester) is thanked for X-Ray crystallographic analysis.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- Reviews: (a) A. R. Allen, E. A. Noten and C. R. J. Stephenson, *Chem. Rev.*, 2022, **122**, 2695–2751; (b) D. M. Whalley and M. F. Greaney, *Synthesis*, 2022, 1908–1918; (c) M. Huynh, M. De Abreu, P. Belmont and E. Brachet, *Chem. – Eur. J.*, 2021, **27**, 3581–3607.
- Selected examples of tandem STRs: (a) Y. Guoren and Z. Zheng, *Synth. Commun.*, 1997, **27**, 1455–1463; (b) M. Pudlo, I. Allart-Simon, B. Tinant, S. Gerard and J. Sapi, *Chem. Commun.*, 2012, **48**, 2442–2444; (c) W. Kong, M. Casimiro, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2013, **135**, 14480–14483; (d) W. Kong, M. Casimiro, N. Fuentes, E. Merino and C. Nevado, *Angew. Chem., Int. Ed.*, 2013, **52**, 13086–13090; (e) M. Tait, M. Donnard, A. Minassi, J. Lefranc, B. Bechi, G. Carbone, P. O'Brien and J. Clayden, *Org. Lett.*, 2013, **15**, 974–976; (f) W. Kong, E. Merino and C. Nevado, *Angew. Chem., Int. Ed.*, 2014, **53**, 5078–5082; (g) C. M. Holden, S. M. A. Sohel and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2016, **55**, 2450–2453; (h) S. Coulibali, E. Deruer, E. Godin and S. Canesi, *Org. Lett.*, 2017, **19**, 1188–1191; (i) D. J. Leonard, J. W. Ward and J. Clayden, *Nature*, 2018, **562**, 105–109; (j) T. M. Monos, R. C. McAtee and C. R. J. Stephenson, *Science*, 2018, **361**, 1369–1373; (k) J. Yu, Z. Wu and C. Zhu, *Angew. Chem., Int. Ed.*, 2018, **57**, 17156–17160; (l) H. L. Barlow, P. T. G. Rabet, A. Durie, T. Evans and M. F. Greaney, *Org. Lett.*, 2019, **21**, 9033–9035; (m) D. M. Whalley, H. A. Duong and M. F. Greaney, *Chem. – Eur. J.*, 2019, **25**, 1927–1930; (n) Z.-S. Wang, Y.-B. Chen, H.-W. Zhang, Z. Sun, C. Zhu and L.-W. Ye, *J. Am. Chem. Soc.*, 2020, **142**, 3636–3644; (o) J. Liu, S. Wu, J. Yu, C. Lu, Z. Wu, X. Wu, X.-S. Xue and C. Zhu, *Angew. Chem., Int. Ed.*, 2020, **59**, 8195–8202; (p) X.-Y. Liu, S.-Y. Tian, Y.-F. Jiang, W. Rao and S.-Y. Wang, *Org. Lett.*, 2021, **23**, 8246–8251; (q) C. Hervieu, M. S. Kirillova, T. Suárez, M. Müller, E. Merino and C. Nevado, *Nat. Chem.*, 2021, **13**, 327–334; (r) D. M. Whalley, J. Seayad and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2021, **60**, 22219–22223; (s) A. R. Allen, J.-F. Poon, R. C. McAtee, N. B. Watson, D. A. Pratt and C. R. J. Stephenson, *ACS Catal.*, 2022, **12**, 8511–8526; (t) N. Radhoff and A. Studer, *Nat. Commun.*, 2022, **13**, 3083–3093; (u) J. Huang, F. Liu, L.-H. Zeng, S. Li, Z. Chen and J. Wu, *Nat. Commun.*, 2022, **13**, 7081–7090; (v) C. Cheibas, N. Fincias, N. Casaretto, J. Garrec and L. El Kaim, *Angew. Chem., Int. Ed.*, 2022, **61**, e202116249; (w) E. A. Noten, R. C. McAtee and C. R. J. Stephenson, *Chem. Sci.*, 2022, **13**, 6942–6949; (x) K. Signo and S. Canesi, *Org. Lett.*, 2022, **24**, 4939–4942; (y) B. Horst, D. S. Verdoorn, S. Hennig, G. van der Heijden and E. Ruijter, *Angew. Chem., Int. Ed.*, 2022, **61**, 202210592; (z) C. He, K. Zhang, D.-N. Wang, M. Wang, Y. Niu, X.-H. Duan and L. Liu, *Org. Lett.*, 2022, **24**, 2767–2771; (aa) T. Sephton, J. M. Large, S. Butterworth and M. F. Greaney, *Org. Lett.*, 2023, **25**, 6736–6740; (ab) D. J. Babcock, A. J. Wolfram, J. L. Barney, S. M. Servagno, A. Sharma and E. D. Nacsa, *Chem. Sci.*, 2024, **15**, 4031–4040; (ac) A. Das, D. L. Myers, V. Ganesh and M. F. Greaney, *Org. Lett.*, 2024, **26**, 2612–2616.
- X.-Q. Chu, D. Ge, Y.-Y. Cui, Z.-L. Shen and C.-J. Li, *Chem. Rev.*, 2021, **121**, 12548–12680.
- (a) E. A. Noten, C. H. Ng, R. M. Wolesensky and C. R. J. Stephenson, *Nat. Chem.*, 2024, **16**, 599–606; (b) C. Hervieu, M. S. Kirillova, Y. Hu, S. Cuesta-Galisteo, E. Merino and C. Nevado, *Nat. Chem.*, 2024, **16**, 607–614.
- T. Sephton, A. Charitou, C. Trujillo, J. M. Large, S. Butterworth and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2023, **62**, e202310583.
- (a) S. B. Blakey and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 6046–6047; (b) S. Ueno, N. Chatani and F. Kakiuchi, *J. Am. Chem. Soc.*, 2007, **129**, 6098–6099; (c) Y. Ma, Y. Pang, S. Chhabra, E. J. Reijerse, A. Schnegg, J. Niski, M. Leutzsch and J. Cornella, *Chem. – Eur. J.*, 2020, **26**, 3738–3743.
- (a) G. Liu, Y. Shen, Z. Zhou and X. Lu, *Angew. Chem., Int. Ed.*, 2013, **52**, 6033–6037; (b) J. Sun, G. Zheng, T. Xiong, Q. Zhang, J. Zhao, Y. Li and Q. Zhang, *ACS Catal.*, 2016, **6**, 3674–3678; (c) J. Park, B. Kang and V. M. Dong, *Angew. Chem., Int. Ed.*, 2018, **57**, 13598–13602.
- P. T. G. Rabet, S. Boyd and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2017, **56**, 4183–4186.
- (a) V. Lupi, M. Penso, F. Foschi, F. Gassa, V. Mihali and A. Tagliabue, *Chem. Commun.*, 2009, 5012–5014; (b) S. Johnson, E. Kovács and M. F. Greaney, *Chem. Commun.*, 2020, **56**, 3222–3224.
- Deposition number 2342281[†] contains the supplementary crystallographic data for compound **17a**.
- P. Gilli, V. Bertolasi, V. Ferretti and G. Gilli, *J. Am. Chem. Soc.*, 2000, **122**, 10405–10417.
- H. Bai, H. Zhang, Y. Guo, H. Chen, D. Wei, S. Li, Y. Zhu and W. Zhang, *Org. Chem. Front.*, 2019, **6**, 125–133.

