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Triflimide-catalysed sigmatropic rearrangement of *N*-allylhydrazones as an example of a traceless bond construction

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The recognition of structural elements (that is, retrons) that signal the application of specific chemical transformations is a key cognitive event in the design of synthetic routes to complex molecules. Reactions that produce compounds without an easily identifiable retron, by way of either substantial structural rearrangement or loss of the atoms required for the reaction to proceed, are significantly more difficult to apply during retrosynthetic planning, yet allow for non-traditional pathways that may facilitate efficient acquisition of the target molecule. We have developed a triflimide (Tf_2NH)-catalysed rearrangement of *N*-allylhydrazones that allows for the generation of a sigma bond between two unfunctionalized sp^3 carbons in such a way that no clear retron for the reaction remains. This new 'traceless' bond construction displays a broad substrate profile and should open avenues for synthesizing complex molecules using non-traditional disconnections.

The [3,3] sigmatropic rearrangements are a particularly powerful class of reactions for the synthesis of complex molecules. For example, the Claisen rearrangement is a powerful fragment coupling reaction that can create an otherwise difficult-to-form carbon–carbon bond by the initial construction of a comparatively easily forged carbon–oxygen bond[1]. Because sigmatropic rearrangements typically involve significant structural reorganization and generate functional groups not present in the starting material, they do not often produce clearly identifiable retrons[2] that signal for their application in the forward sense during the planning stages of any synthetic endeavour. Recognition and implementation of such reactions can, however, lead to highly inventive and non-traditional approaches to complex molecules, such as the spectacular demonstration by Shair and colleagues in their synthesis of (+)-CP-263,114 (ref. 3). It was within the context of devising unique fragment couplings to facilitate synthesis along non-traditional pathways that we became interested in the sigmatropic rearrangement of *N*-allylhydrazones. These compounds undergo a unique [3,3] sigmatropic rearrangement followed by dinitrogen extrusion to generate products that bear no resemblance to the starting materials, a process that we term 'traceless bond construction'. The general concept of a traceless bond construction is outlined in Fig. 1a, in which two functional groups are shown to react to form a new compound that undergoes a subsequent reaction with loss of the remaining functional group. In essence, a new sigma bond is formed at a location where there is no remaining functionality. In 1973, Stevens and colleagues reported the low yield and limited thermal rearrangement of *N*-allylhydrazones (Fig. 1b), a reaction that has seen virtually no use by synthetic chemists[4]. Given that the generation of hydrazones is typically a high-yielding and facile process, we considered the two-step transformation (that is, **1** → **3**) to have significant potential for carbon–carbon bond fragment coupling. As an additional benefit, the usefulness of the coupling reaction manifests itself further in that there are no post-reaction functional groups that need to be manipulated as part of an ongoing synthesis. This general type of reactivity is common for many hydrazone-based transformations[5–9]. Despite the significant potential impact of this reaction on synthetic chemistry at both a strategic and practical level, it has remained undeveloped for over 35 years due to a limited substrate scope, the requirement for high temperatures and low yields. In 2006, we initiated a research programme aimed at unlocking the potential of *N*-allylhydrazones[10,11]. We now report the successful development of a triflimide (Tf_2NH)-catalysed variant of the Stevens [3,3] sigmatropic rearrangement (**4** → **5**, Fig. 1c) that displays a significantly

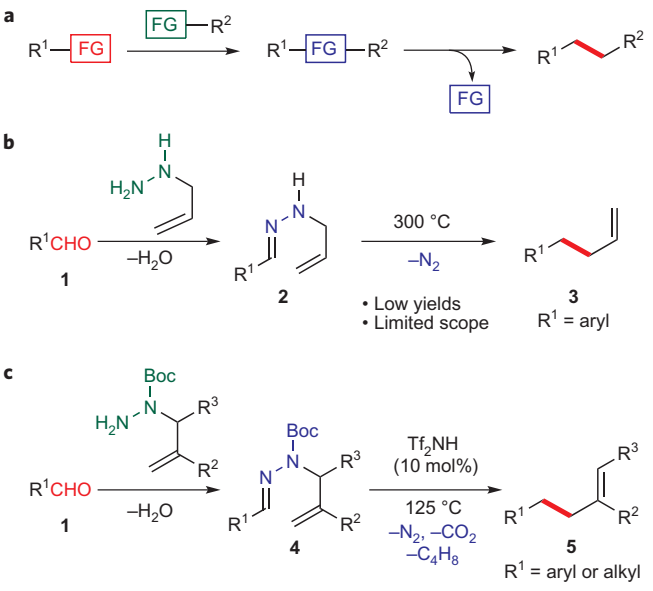

Figure 1 | Traceless bond constructions of *N*-allylhydrazones. a, General concept of a traceless bond construction, in which functional groups (FG) present within the starting material are excised during the course of carbon–carbon bond formation. **b**, Original rearrangement developed by Stevens and colleagues in 1973, which required very harsh conditions and had a low yield. **c**, Triflimide-catalysed rearrangement, demonstrating its wider scope and higher yields. Tf, trifluoromethanesulfonyl; Boc, *t*-butyl carbamate.

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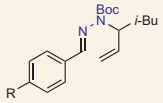
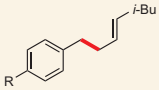
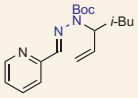
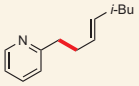
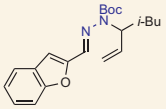
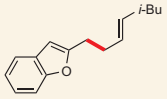
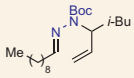
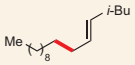
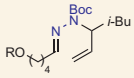
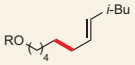
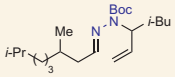
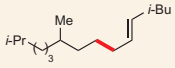
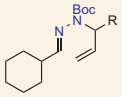
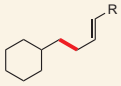
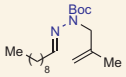
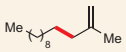
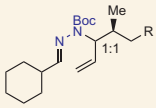
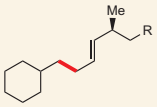
Table 1 | Substrate scope of triflimide-catalysed traceless bond construction.

Entry	Substrate (4)		Product (5)		Yield (%)*	*E*:*Z*†
1		**4a** R = H **4b** R = *i*-Pr **4c** R = Br		**5a** R = H **5b** R = *i*-Pr **5c** R = Br	66 74 75	>20:1 >20:1 >20:1
2		**4d**		**5d**	49	>20:1
3		**4e**		**5e**	75	>20:1
4		**4f**		**5f**	60	6:1
5		**4g** R = TBDPS **4h** R = Bn		**5g** R = TBDPS **5h** R = Bn	57 63	12:1 5:1
6		**4i**		**5i**	65	6:1
7		**4j** R = H **4k** R = Me **4l** R = Et **4m** R = *n*-Pr **4n** R = *i*-Bu **4o** R = *i*-Pr		**5j** R = H **5k** R = Me **5l** R = Et **5m** R = *n*-Pr **5n** R = *i*-Bu **5o** R = *i*-Pr	0 53 54 69 70 63	— 4:1 5:1 8:1 7:1 8:1
8		**4p**		**5p**	51	—
9		**4q** R = Me **4r** R = OBn		**5q** R = Me **5r** R = OBn	55 51	12:1 17:1

Standard conditions: 0.5 mmol **4**, 10 mol% Tf_2NH, 0.05 M diglyme, 125 °C, 0.25–2 h. *Isolated yield. †Determined by ^1H NMR spectroscopy or GC.
Boc, *t*-butyl carbamate; Me, methyl; Et, ethyl; Bu, butyl; Pr, propyl; Bn, benzyl; TBDPS, *t*-butyldiphenylsilyl; Tf, trifluoromethanesulfonyl.

improved substrate scope and holds broad promise for applications in synthesis.

Results

During our initial studies[10], we discovered that treating *N*-allylhydrazones such as **4** with stoichiometric copper(II) chloride ($CuCl_2$) resulted in a previously unknown carbon–carbon and carbon–chlorine bond forming reaction. Although this discovery was interesting, we wished to return to our original goal of establishing a useful variant of the original Stevens process. An investigation of metal complexes other than $CuCl_2$ provided few useful outcomes, but revealed that hafnium(IV) trifluoromethanesulfonate produced some of the desired product at 125 °C. Trifluoromethanesulfonic acid alone was more effective than the metal triflate, and after further investigations into Brønsted acids we found that 10 mol% triflimide in diethylene glycol dimethyl ether (diglyme) at 125 °C produced the best yields across a range of substrates (Table 1). Triflimide has found significant use as a catalyst for a wide range of transformations[12].

The reaction proved tolerant of hydrazone substrates derived from aromatic aldehydes (Table 1, entry 1), including heterocyclic systems (entries 2 and 3), providing the coupled products in good yield and in a >20:1 ratio of *E*- to *Z*-isomers. Our earlier work on hydrazone rearrangements only worked well for hydrazones derived from aromatic aldehydes; aliphatic systems resulted in multiple decomposition products. Given this background, we were anxious to demonstrate a wider substrate scope for the new transformation. The hydrazone derived from decanal (**4f**) was therefore prepared and exposed to the triflimide reaction conditions (entry 4). Smooth rearrangement ensued, and the desired adduct **5f** was isolated in a yield of 60% (6:1, *E*:*Z*). The presence of the *t*-butyl carbamate (Boc) group was crucial to the success of this rearrangement; aliphatic hydrazones lacking the Boc-group proved difficult to prepare with high purity and were unstable in the presence of air.

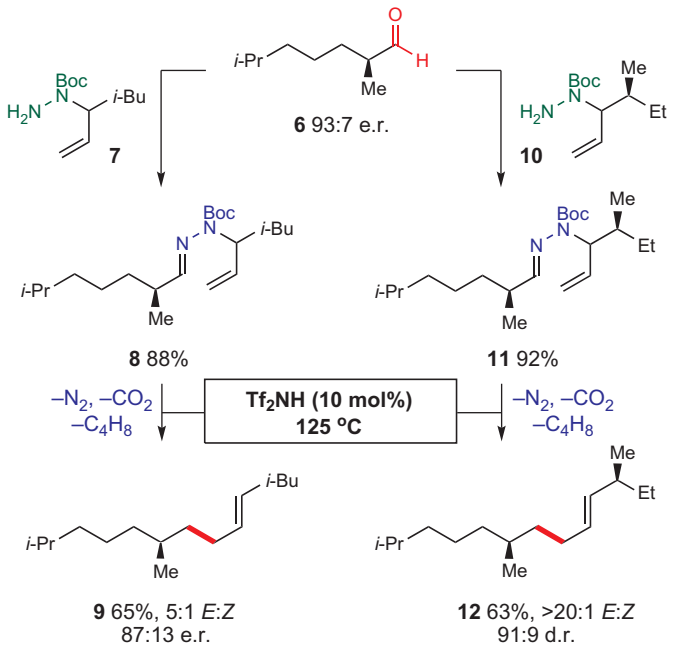


Figure 2 | Impact of resident stereocentres. The extent to which hydrazones possessing a stereocentre might undergo scrambling under the reaction conditions was examined. Hydrazones **8** and **11** undergo traceless bond construction to give products **9** and **12**, respectively. In each case, the loss of stereochemical integrity of the potentially labile methyl stereocentre was shown to be minimal, indicating that this chemistry could find use in the synthesis of complex acyclic molecules. Boc, *t*-butyl carbamate; Me, methyl; Et, ethyl; Bu, butyl; Tf, trifluoromethanesulfonyl.

On the other hand, aryl aldehyde-derived hydrazones lacking the Boc-group were prepared readily, but resulted in multiple products and low yields when exposed to 10 mol% triflimide at elevated temperatures.

Functionalized substrates were tolerant of the reaction conditions; hydrazones containing a primary *t*-butyldiphenylsilyl (TBDPS) or benzyl (Bn) ether resulted in 57% and 63% yields, respectively (Table 1, entry 5). Use of the more acid-labile *p*-methoxybenzyl (PMB) ether resulted in significant decomposition, indicating that the current chemistry remains limited to those substrates containing functional groups that are stable under acidic conditions. β-Substitution on the aldehyde component was well tolerated (entry 6). Using hydrazones derived from cyclohexanecarboxaldehyde, we explored the use of various *N*-allylhydrazide fragments (entry 7). The parent allyl-based hydrazone **4j** underwent significant decomposition and failed to provide the desired product (**5j**, R = H). Alkyl substitution at the 1-position of the hydrazide was compatible with the conditions (entry 7, **5k–o**, R = Me, Et, *n*-Pr, *i*-Bu, *i*-Pr), providing the (*E*)-1,2-disubstituted adducts between 53 and 70% yield. Methyl substitution at the 2-position of the hydrazide fragment produced the corresponding 1,1-disubstituted alkene **5p** in 51% yield (entry 8). We next synthesized the non-racemic *N*-allylhydrazides derived from the (*S*)-2-methylbutan-1-ol and the Roche ester (that is, methyl (*S*)-3-hydroxy-2-methylpropionate), which were each condensed with cyclohexanecarboxaldehyde to provide hydrazones **4q** and **4r** (Table 1, entry 9). The hydrazones thus formed were mixtures of diastereomers at the nitrogen-bearing stereocentre, but this proved to be inconsequential, because each rearranged in greater than 50% yield (≥12:1, *E*:*Z*). These last two entries clearly demonstrate the usefulness of this new traceless bond construction for the stereoselective synthesis of alkenes having allylic stereogenic centres.

A more pressing issue to address was whether a substrate derived from an enantio-enriched aldehyde having an α-stereocentre would racemize under the acidic reaction conditions of the sigmatropic rearrangement (Fig. 2). To answer this question, we prepared chiral enantio-enriched hydrazone **8** from the corresponding aldehyde **6** (93:7 e.r.) (ref. 13). The use of a racemic hydrazine fragment (**7**) meant that hydrazone **8** was formed as a mixture of diastereomers. Exposure of this mixture to our standard conditions for the triflimide-catalysed process resulted in the formation of the desired product with a yield of 65% and minimal erosion of optical purity over the two steps from aldehyde **6**. Finally, we prepared a hydrazone with a methyl-bearing stereocentre on each component (that is, **11**). This substrate underwent the desired rearrangement with a yield of 63% (>20:1, *E*:*Z*; 91:9 d.r.), providing a new compound with two stereogenic centres positioned in a 1,6-relationship.

Discussion

Two reasonable pathways may be considered for this acid-catalysed rearrangement (Fig. 3). The first (Path A) proceeds with initial loss of the Boc-group to generate a protonated species such as **II**, which would undergo bond reorganization to produce **III** and eventually the final product, via diazene **IV**, which would readily extrude dinitrogen[14]. Given the poor results obtained for hydrazones lacking the Boc-group, we speculate that carbon–carbon bond formation might precede decomposition of the Boc-group (Path B). In this alternative pathway, rearrangement of protonated hydrazone **V** would produce **VI**, which would lose the Boc-group to generate diazene **IV**. Formation of the (*E*)-alkene as the major isomer in all cases is most likely due to the reaction proceeding through a chair-like cyclic transition state similar to that postulated for our previously reported *N*-allylhydrazone-based transformations[10,11]. We speculated that perhaps the olefin ratios observed were due to a thermodynamic equilibration of the alkene isomers under the acidic reaction conditions, but observed no such isomerization when pure (*Z*)-2-methylhexadec-4-ene was exposed to the reaction conditions.

At a strategic level, this new bond construction opens new avenues for synthesis using disconnections that are not traditionally applied by synthetic chemists. For the molecule indicated in Fig. 4, the most obvious disconnection point is at the π-bond (***a***) in the form of an olefination transform. Similarly, if one chose to disconnect adjacent to the sp^2 carbon (***b***), a metal-based coupling could

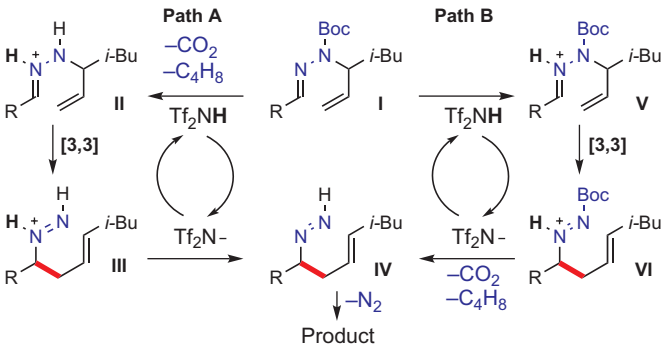


Figure 3 | Possible reaction pathways for traceless bond construction. The working hypothesis for plausible reaction pathways is shown. In Path A, the Boc-group is lost first to produce **II**, which then undergoes C–C bond rearrangement to generate **III**, and then the product via intermediate diazene **IV**. In Path B, C–C bond formation precedes loss of the Boc-group (that is, **V** to **VI** to **IV**). Reactions involving hydrazones lacking the Boc-group produced poor results, providing some circumstantial evidence that Path B may be favoured, but further studies are required to establish this definitively. Boc, t-butyl carbamate; Bu, butyl; Tf, trifluoromethanesulfonyl.

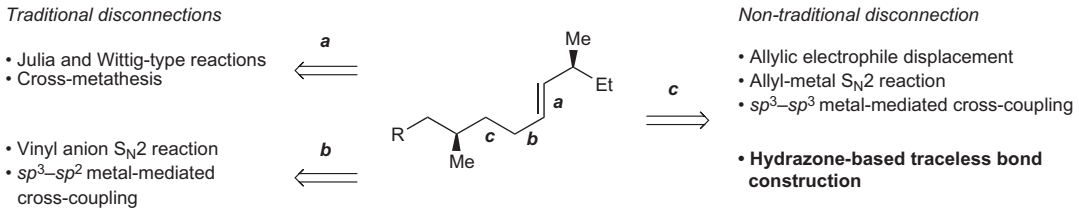


Figure 4 | Analysis of strategic bond disconnections: new avenues for synthesis using a non-traditional disconnection. Analysis of the fictive target shown reveals three major points of disconnection. Bond ***a*** lends itself to construction by means of a Julia- or Wittig-type olefination, or through olefin cross-metathesis. Carbon bond ***b*** may potentially be formed by an SN2 reaction or by the more modern sp^3–sp^2 metal-mediated cross-coupling. In general, bonds ***a*** and ***b*** are typical choices for synthetic chemists, whereas disconnection at bond ***c*** is not as common due to less developed or unreliable methods. The hydrazone-based traceless bond construction enables convergent fragment assembly at bond ***c*** and thus opens avenues for alternative syntheses along non-traditional paths. Me, methyl; Et, ethyl.

occur. Disconnection at the allylic position (***c***) would traditionally be a poorer strategic choice, because formation of this bond using either an allyl electrophile or an allyl nucleophile raises issues of regiocontrol and product alkene geometry. Recent methods for transition metal-mediated sp^3–sp^3 cross-coupling do, however, offer a solution to this problem for many cases[15–17]. The reaction we have developed also enables such a disconnection to be made with a high level of confidence; the condensation step is straightforward, and the sigmatropic rearrangement is completely regioselective and displays good levels of stereoselectivity. Furthermore, the concept of traceless reactions represents a powerful approach to the design of complex molecules and provides enhanced options for the synthetic chemist engaged in target directed synthesis. Future efforts in this area will be focused on the requirement for high temperatures and a strong acid in the reaction, enabling a significantly enhanced substrate scope, particularly regarding substrates bearing acid-sensitive functional groups.

The reaction we have developed is applicable to a wide range of substrates, including aromatic and aliphatic hydrazones, and those possessing stereogenic centres. From a synthetic standpoint, the transformation offers a unique means for constructing a σ-bond between two unfunctionalized sp^3 carbons, while simultaneously generating a stereo-defined alkene. Moreover, because this reaction forms products that do not contain an obvious retron, its synthetic application has the potential to lead to novel and creative pathways that are not immediately obvious. Continued research in this area should unveil more such traceless bond constructions and facilitate synthesis along non-traditional routes.

Methods

General procedure for the traceless bond construction. Triflimide (0.25 M in CH_2Cl_2, 200 μl, 0.05 mmol) was added to a flame-dried 25-ml round-bottomed flask containing a magnetic stir bar under a N_2 atmosphere. The CH_2Cl_2 was removed by vigorously purging the flask with N_2 until dry crystalline triflimide was visible in the reaction flask. The N_2 flow rate was decreased and diglyme (5.0 ml) was added to the reaction flask. A solution of the requisite hydrazone (0.50 mmol) in diglyme (2.5 ml + 2.5 ml rinse) was then added to this, via a cannula, at room temperature under a N_2 atmosphere. The reaction flask was fitted with a reflux condenser and purged with N_2. The reaction was then stirred at 125 °C until deemed complete by thin layer chromatography (30% EtOAc/hexanes, *p*-anisaldehyde stain). After cooling to room temperature the reaction was washed into a separatory funnel with hexanes (20 ml) and diluted with sat. $NaHCO_3$ (15 ml) and H_2O (100 ml). The aqueous phase was removed and the organic phase was washed with sat. NaCl (15 ml) and H_2O (100 ml). The combined aqueous phases were extracted with hexanes (10 ml) and the combined organic phases were dried over Na_2SO_4 and concentrated to produce a yellow oil. Flash column chromatography on silica gel resulted in the alkene product.

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References

1. Castro, A. M. M. Claisen rearrangement over the past nine decades. *Chem. Rev.* **104,** 2939–3002 (2004).
2. Corey, E. J. & Cheng, X.-M. *The Logic of Chemical Synthesis* (Wiley, 1989).
3. Chen, C., Layton, M. E., Sheehan, S. M. & Shair, M. D. Synthesis of (+)-CP-263,114. *J. Am. Chem. Soc.* **122,** 7424–7425 (2000).
4. Stevens, R. V., McEntire, E. E., Barnett, W. E. & Wenkert, E. Thermally induced [3,3] sigmatropic rearrangement of *N*-allylhydrazones. *Chem. Commun.* 662–663 (1973).
5. Vedejs, E. & Stolle, W. T. Reductive alkylation of aldehyde tosylhydrazones with organolithium reagents. *Tetrahedron Lett.* **18,** 135–138 (1977).
6. Bertz, S. H. The preparation of hindered cuprates from aldehyde tosylhydrazones. *Tetrahedron Lett.* **21,** 3151–3154 (1980).
7. Myers, A. G. & Kukkola, P. J. Stereoselective synthesis of olefins from silylated sulfonylhydrazones. *J. Am. Chem. Soc.* **112,** 8208–8210 (1990).
8. Myers, A. G. & Movassaghi, M. Highly efficient methodology for the reductive coupling of aldehyde tosylhydrazones with alkyllithium reagents. *J. Am. Chem. Soc.* **120,** 8891–8892 (1998).
9. Barluenga, J., Tomás-Gamasa, M., Aznar, F. & Valdés, C. Metal-free carbon–carbon bond-forming reductive coupling between boronic acids and tosylhydrazones. *Nature Chem.* **1,** 494–499 (2009).
10. Mundal, D. A., Lee, J. J. & Thomson, R. J. Tandem carbon–carbon and carbon–chlorine bond formation by Cu(II) chloride-promoted [3,3] sigmatropic rearrangement of *N*-allylhydrazones. *J. Am. Chem. Soc.* **130,** 1148–1149 (2008).
11. Mundal, D. A., Lutz, K. E. & Thomson, R. J. Stereoselective synthesis of dienes from *N*-allylhydrazones. *Org. Lett.* **11,** 465–468 (2009).
12. Akiyama, T. Stronger Brønsted acids. *Chem. Rev.* **107,** 5744–5758 (2007).
13. Taber, D. F. & Houze, J. B. The 2-hydroxycitronellols, convenient chirons for natural products synthesis. *J. Org. Chem.* **59,** 4004–4006 (1994).
14. Myers, A. G., Movassaghi, M. & Zheng, B. Mechanistic studies of the free-radical fragmentation of monoalkyl diazenes. *Tetrahedron Lett.* **38,** 6569–6572 (1997).
15. Saito, B & Fu, G. C. Alkyl–alkyl Suzuki cross-couplings of unactivated secondary alkyl halides at room temperature. *J. Am. Chem. Soc.* **129,** 9602–9603 (2007).
16. Saito, B & Fu, G. C. Enantioselective alkyl–alkyl Suzuki cross-couplings of unactivated homobenzylic halides. *J. Am. Chem. Soc.* **130,** 6694–6695 (2008).
17. Son, S. & Fu, G. C Nickel-catalyzed asymmetric Negishi cross-couplings of secondary allylic chlorides with alkylzincs. *J. Am. Chem. Soc.* **130,** 2756–2757 (2008).

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Author contributions

R.J.T. conceived the idea and wrote the manuscript. D.A.M. and C.T.A. performed the experiments. All the authors analysed the data, contributed to discussions and edited the manuscript.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/. Correspondence and requests for materials should be addressed to R.J.T.