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Intermolecular scandium triflate-promoted nitrene-transfer [5 + 1] cycloadditions of vinylcyclopropanes†

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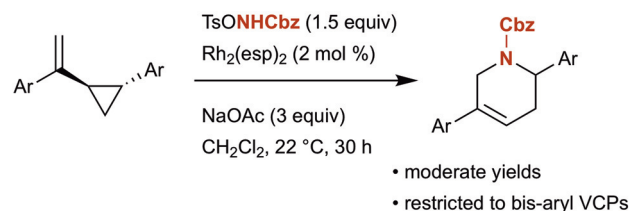
Sc(OTf)₃-promoted [5 + 1] cycloaddition of vinylcyclopropanes with PhINTs is reported, enabling the regioselective preparation of a range of 1,2,3,6-tetrahydropyridine scaffolds under mild conditions. This represents the second example of a [5 + 1] nitrene-transfer cycloaddition and exhibits complementary substrate scope to the antecedent work, expanding the range of N-heterocycles accessible via this strategy.

Nitrogen-containing heterocycles are prevalent in FDA-approved pharmaceuticals,¹ and as a result, new methods and strategies for their synthesis are needed to facilitate the more rapid introduction of new therapeutics.² In particular, control of regio- and stereoselectivity of substitution patterns not readily accessible through other means is a prime concern. To this end, cycloaddition and annulation approaches are preferred strategies with the potential to exert the desired control. The use of nitrogen as a one-atom component, in various forms including amines, amides, carbamates, sulfonamides, and oxidized forms thereof can be advantageous due to the wide commercial availability and/or ease of preparation of precursors bearing these functional groups.³

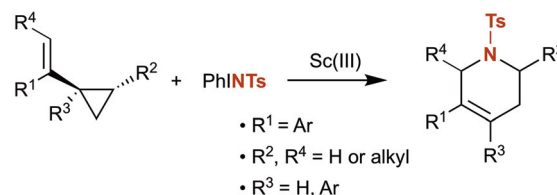
One class of reactions having these attributes are those that involve nitrenes or nitrene equivalents as reactive intermediates. It has been demonstrated, for example, that Cu(II) catalysis,⁴ Ti(II)/Ti(IV) redox catalysis,⁵ Ru catalysis,⁶ vanadium(III) catalysis,⁷ and stoichiometric BF₃⁸ can enable formal intermolecular cycloadditions between hydrocarbons or other components and pre-oxidized aniline or sulfonamide nitrene precursors, but these reports focus entirely on the synthesis of five-membered N-heterocycles. Expanding on this burgeoning area of research, we recently reported the first examples of

nitrene-transfer cycloaddition leading to six-membered ring products (Scheme 1a).⁹ Specifically, a Rh(II)-catalyzed formal [5 + 1] cycloaddition between benzyl (tosyloxy)carbamate and vinylcyclopropanes (VCPs)¹⁰ provided tetrahydropyridine products with high regioselectivity. Furthermore, these products could be elaborated to complex piperidines, the most common N-heterocycle in FDA-approved drugs.¹ This method, though, is limited to substrates bearing aryl substituents on both the olefin and cyclopropane ring of the VCP at the specific positions indicated for generic substrate **1**. Due to our continued interest in this new approach for heterocycle synthesis, we have endeavored to develop conditions that are compatible with a more diverse array of VCPs. Herein, we describe a novel scandium-catalyzed [5 + 1] reaction between VCPs and [N-(p-toluenesulfonyl)imino]phenyliodinane (PhINTs) that circumvents the requirement for aryl substitution of the cyclopropane ring. This method exhibits complete complementarity to the previous Rh-catalyzed method, and provides initial mechanistic insight that could help guide the development of [5 + 1]

A. Previous work: Rh(II)-catalyzed [5+1] cycloaddition, ref. 9.



B. This work: Sc(III)-promoted [5+1] cycloaddition.



Scheme 1 [5 + 1] nitrene-transfer cycloaddition.

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cycloadditions into a general approach for the preparation of heterocyclic products.

We began with VCP **1a**, lacking an aryl substituent on the vinylcyclopropane ring, and which does not provide the product **2a** using the previously developed $\text{Rh}_2(\text{esp})_2$ -catalyzed conditions, nor any other Rh-catalyzed previously explored. In an initially promising result, reaction of **1a** with PhINTs under typical conditions for Cu(II)-promoted olefin aziridination¹¹ provided tetrahydropyridine **2a** as the major product (Table 1, entry 1). One limitation of this approach was a requirement to use the nitrenoid precursor as the limiting reagent to achieve reasonable yields (entry 2). This prompted additional investigations, revealing that a variety of Brønsted and Lewis acids (e.g. entries 5–7) could be employed to effect the same overall transformation. Ultimately, the use of $\text{Sc}(\text{OTf})_3$ proved to be the most amenable to optimization of other variables.¹² The final conditions (2.5 equiv. PhINTs, 0.5 equiv. $\text{Sc}(\text{OTf})_3$, CH_2Cl_2 , 4 °C) employ slow addition of a solution of the VCP over one hour to achieve the highest yields of the cycloaddition product in 2 hours of total reaction time (entry 13). To rule out trace amounts of Brønsted acid as the catalyst under these conditions, we performed a control experiment using 1 mol% of triflic acid and observed only trace amounts of product formation (entry 17). This result is consistent with the additional observation that the use metal triflate salts other than $\text{Sc}(\text{OTf})_3$ largely failed to produce reasonable amounts of the desired product (entries 14–16), pointing toward a critical role for Sc(III).¹³

Table 1 Optimization of the [5 + 1] reaction^a

Entry	Equiv. VCP	Equiv. PhINTs	Temp.	Acid (equiv.)	Yield (%)
1	3	1	rt	$\text{Cu}(\text{OTf})_2$ (0.5)	47
2	1	1	rt	$\text{Cu}(\text{OTf})_2$ (0.5)	20
3	1	1	rt	$\text{Cu}(\text{OTf})_2$ (1.0)	13
4	1	1	4 °C	TfOH (1.0)	41
5	1	1	4 °C	TfOH (0.5)	20
6	1	1	4 °C	$\text{HBF}_4 \cdot \text{OEt}_2$ (2.0)	38
7	1	1	−10 °C	$\text{BF}_3 \cdot \text{OEt}_2$ (1.0)	30 ^b
8	1	1	rt	$\text{Sc}(\text{OTf})_3$ (1.0)	22
9	1	1	rt	$\text{Sc}(\text{OTf})_3$ (0.5)	24
10	1	1	4 °C	$\text{Sc}(\text{OTf})_3$ (0.5)	29
11	1	1.5	4 °C	$\text{Sc}(\text{OTf})_3$ (0.5)	38
12	1 ^c	1.5	4 °C	$\text{Sc}(\text{OTf})_3$ (0.5)	45
13	1 ^c	2.5	4 °C	$\text{Sc}(\text{OTf})_3$ (0.5)	58
14	1 ^c	2.5	4 °C	$\text{Cu}(\text{OTf})_2$ (0.5)	17 ^b
15	1 ^c	2.5	4 °C	$\text{Zn}(\text{OTf})_2$ (0.5)	0 ^b
16	1 ^c	2.5	4 °C	$\text{Yb}(\text{OTf})_3$ (0.5)	5 ^b
17	1 ^c	1	4 °C	TfOH (0.01)	<5 ^b

^a All reactions were conducted on a 0.2 mmol scale in the limiting reagent, with isolated yields reported except where noted. ^b NMR yield.

^c A solution of VCP **1a** in CH_2Cl_2 was added dropwise over 1 h.

Having established optimized conditions for the [5 + 1] cycloaddition of **1a**, we turned our attention to investigating the effect of variations of the VCP structure, focusing on the R^1 , R^2 , and R^3 positions as indicated in Fig. 1. Evaluation of the $\text{Sc}(\text{OTf})_3$ -promoted conditions revealed that yields were highly sensitive to the nature of the R^1 substituent. In this position, aryl substitution was required for successful formation of the [5 + 1] product. Substitution at the *para* and *meta* positions of the R^1 phenyl group was tolerated. Moreover, a preference for substitution with strongly deactivating (e.g. **2c**) over strongly activating groups was observed, with a *p*-OMe group promoting complete and non-selective conversion of the starting material to a complex mixture of products not including the desired tetrahydropyridine. The use of a trisubstituted olefin led to reduced yield in the formation of tricyclic product **2i**. A key feature of these reactions is that only one olefin regio-

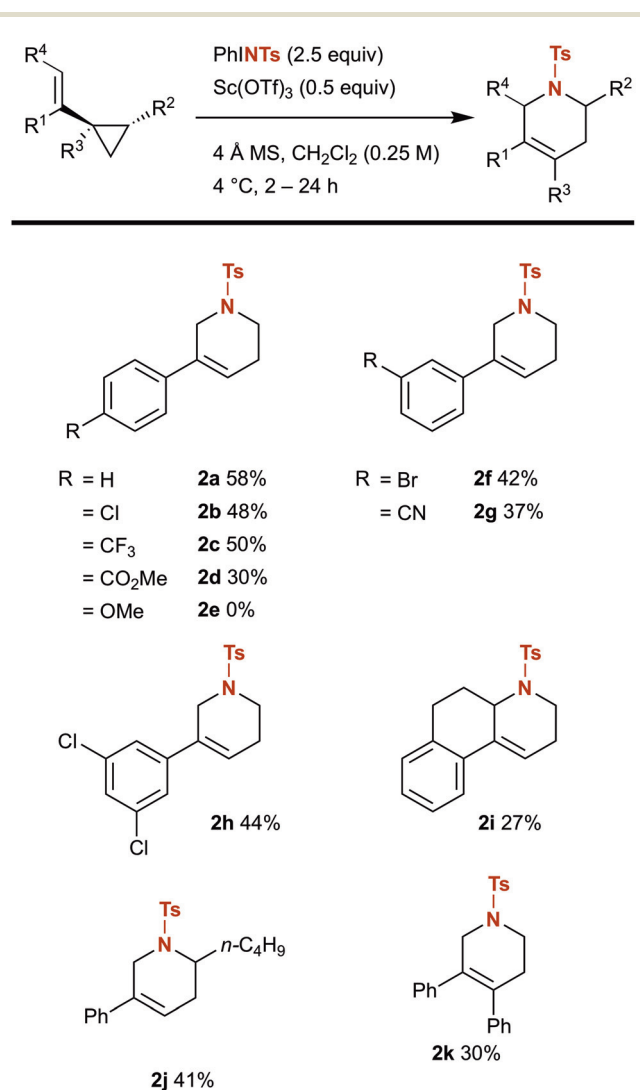
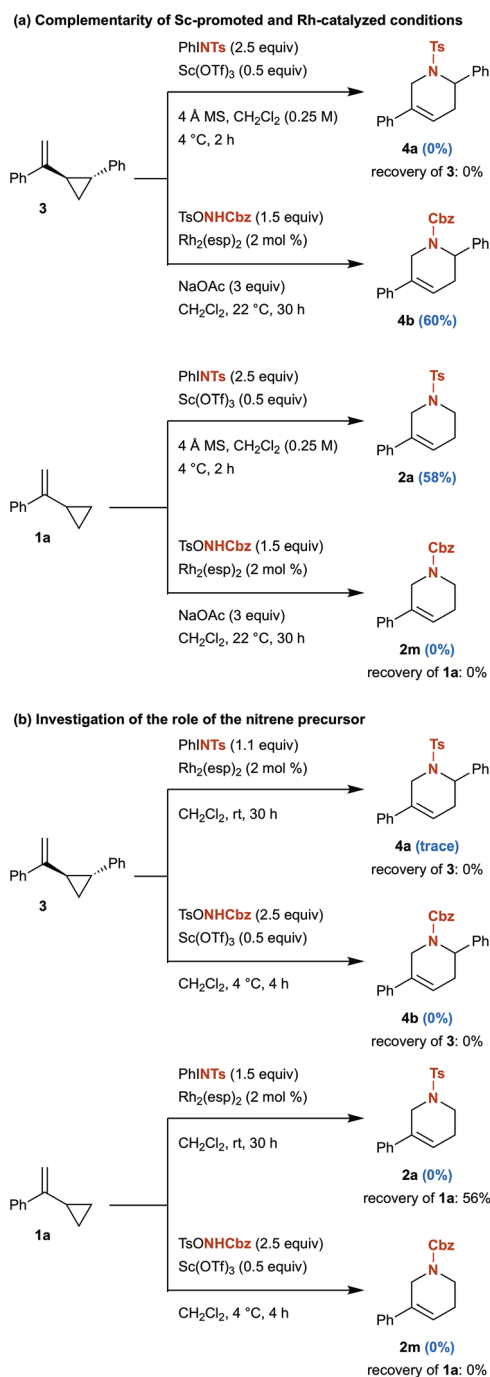


Fig. 1 Scope and limitations of the [5 + 1] cycloaddition. Yields shown are of isolated products. The substrate was added to a mixture of the other reagents over 1 h. Reactions were monitored by TLC and quenched once full consumption of the substrate was observed.

isomer of the [5 + 1] product is observed. Evaluating the effect of alkyl substitution at R², we observed that this regioisomeric preference extends to a high selectivity for the formation of the 2,5-disubstituted rather than 3,5-disubstituted product (*e.g.* **2j**), arising from cleavage of the more substituted cyclopropane C–C bond. In this case, the observation of only one regioisomer is notable given that cleavage of the less substituted bond is clearly feasible in other cases (*vide supra*). In a related experiment, a VCP bearing a phenyl group at the R¹ position and a cyclohexyl group at the R² position (not shown) generated the [5 + 1] product in very low yield (7%), suggesting that the reaction is highly sensitive to steric effects at the R² position. Substitution at the R³ position is tolerated, allowing access to a 2,3-disubstituted product (as in **2k**), albeit in reduced yield. Adding to the synthetic utility of this reaction, methods have been reported that are capable of stereoselectively elaborating both monosubstituted tetrahydropyridines such as **2a** (*via* enantioselective hydrogenation)¹⁴ and 2,5-disubstituted tetrahydropyridines such as **2j** (*via* diastereoselective epoxidation)⁹ to complex bio-relevant piperidines.

Intriguingly, this Sc(OTf)₃-promoted nitrene-transfer cycloaddition exhibits substrate scope that completely differentiates it from our previously reported Rh-catalyzed method.⁹ In the case where R¹ and R² are both phenyl groups, the Rh₂(esp)₂-catalyzed reaction successfully produces product **4a**, whereas use of Sc(OTf)₃/PhINTs as reported here results in degradation of the starting material to a complex mixture of products. This remains true for all other bis-aryl substrates of this class that were evaluated (Scheme 2a). Conversely, substrate **1a** as well as all other substrates evaluated as shown in Fig. 1 fail to provide any products using the Rh-catalyzed conditions. To evaluate the role of the nitrene precursor in these complementary results, we also investigated the use of PhINTs/Rh₂(esp)₂ and TsONHCBz/Sc(OTf)₃ reagent/catalyst combinations (Scheme 2b). In each of the four cases evaluated, this resulted in a failed reaction, providing no isolable amounts of the desired products and, in three out of the four cases, leading to complete non-selective consumption of the starting material. This indicates that the differences in reactivity are not due solely to either the choice of catalyst or nitrene precursor, but are reliant on the specific combination of reagents discovered *via* reaction optimization. Collectively, these results would seem to be indicative of substantial mechanistic differences between the two conditions. Therefore, we set out to further understand the reasons behind these contrasting results.

The Rh-nitrenoid generated as the active oxidant in Rh(II)-catalyzed nitrene transfer reactions is postulated to possess sufficient Lewis acidity to promote ring-opening of *N*-tosyl aziridines to zwitterionic intermediates,¹⁵ which we exploited in the development of the Rh-catalyzed [5 + 1]. That reaction is proposed to proceed through a cyclopropylcarbinyl cation,¹⁶ generated upon nitrene transfer to the olefin of the VCP, that subsequently undergoes rearrangement to the observed product.⁹ In contrast, there are no prior reports of scandium-promoted nitrene transfer and, by extension, no prior mechanistic studies on which to base our investigations of the mecha-



Scheme 2 Control experiments to investigate the complementarity of Sc-promoted and Rh-catalyzed conditions and the role of the nitrene precursor.

nism of the Sc(OTf)₃-promoted [5 + 1]. As demonstrated in Table 1, Cu(OTf)₂ is also capable of promoting the [5 + 1] reaction of **1a**. Like in the case of Sc(OTf)₃, we observe the same complementarity of substrate scope when comparing the copper-promoted and rhodium-catalyzed conditions. In the case of Cu(OTf)₂, evidence gathered by Evans suggests that the non-stereospecific reaction of styrenes with Cu-nitrenoids proceeds through radical intermediates.¹¹ To evaluate whether

this is also the case for $\text{Sc}(\text{OTf})_3$ we attempted a $[5 + 1]$ reaction of **1a** in the presence of the radical scavenger TEMPO (Scheme 3a). This additive completely shut down the $[5 + 1]$ pathway. In addition, we obtained NMR and HRMS evidence of TEMPO adduct **5**.¹⁷ Based on these observations, we propose the mechanism outlined in Scheme 3b. Scandium-promoted nitrene transfer to the VCP could lead, either directly or *via* an aziridine intermediate,¹⁸ to benzylic radical **6**, as is evident from the formation of **5**. Cyclopropylcarbinyl rearrangement¹⁹ would then provide intermediate **7**, which, after ring closure, would provide the observed product. This mechanism is consistent with the observed regioselectivity of olefin formation as well as in the substitution pattern observed for product **2j**, presumably due to favorable C–C bond homolysis to the more stable secondary radical in the latter case. Moreover, the possibility that this class of reactions could occur on a spectrum of polar *vs.* radical character might provide a satisfactory explanation for the complementary selectivity observed for the Rh(II) *vs.* Sc(III)-promoted reactions.

In summary, we have developed a new nitrene-transfer $[5 + 1]$ cycloaddition between vinylcyclopropanes and PhINTs promoted by $\text{Sc}(\text{OTf})_3$. This approach eliminates the requirement for aryl substituted cyclopropanes and allows access to products distinct from our previously reported method, thereby expanding the structural diversity of nitrogen-containing heterocycles accessible *via* this strategy. Mechanistic

studies indicating the stepwise, radical nature of this transformation help to rationalize these improvements in scope. Overall, this report further cements nitrene-transfer $[5 + 1]$ as an emerging class of useful reactions for tetrahydropyridine synthesis, and, along with the previous Rh-catalyzed method, provides a firm basis on which to continue to develop cycloadditions of this type as a general entry to the regiocontrolled synthesis of heterocycles.

Conflicts of interest

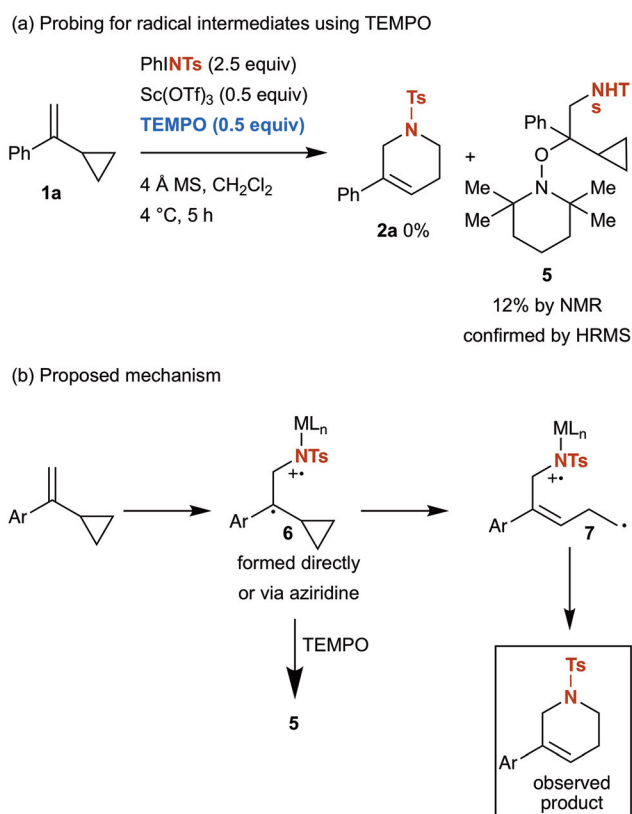
There are no conflicts to declare.

Acknowledgements

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Notes and references

- 1 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
- 2 (a) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson and A. Wood, *Nat. Chem.*, 2018, **10**, 383; (b) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752.
- 3 For recent examples see: (a) J. A. Malone, C. E. Toussell, F. R. Fronczek and R. Kartika, *Org. Lett.*, 2019, **21**, 3610; (b) W. Liu, C. Chen, P. Zhou and H. Tan, *Org. Lett.*, 2017, **19**, 5830; (c) S. Kramer and G. C. Fu, *J. Am. Chem. Soc.*, 2015, **137**, 3803; (d) Q. Zheng and R. Hua, *Tetrahedron Lett.*, 2010, **51**, 4512; (e) W. Liu, H. Jiang and L. Huang, *Org. Lett.*, 2010, **12**, 312.
- 4 Q. Wu, J. Hu, X. Ren and J. Zhou, *Chem. – Eur. J.*, 2011, **17**, 11553.
- 5 (a) Z. W. Gilbert, R. J. Hue and I. A. Tonks, *Nat. Chem.*, 2016, **8**, 63; (b) H.-S. Chiu and I. A. Tonks, *Angew. Chem., Int. Ed.*, 2018, **57**, 6090; (c) Z. W. Davis-Gilbert, X. Wen, J. D. Goodpaster and I. A. Tonks, *J. Am. Chem. Soc.*, 2018, **140**, 7267.
- 6 K. Matsui, M. Shibuya and Y. Yamamoto, *Commun. Chem.*, 2018, **1**, 21.
- 7 K. Kawakita, E. P. Beaumier, Y. Kakiuchi, H. Tsurugi, I. A. Tonks and K. Mashima, *J. Am. Chem. Soc.*, 2019, **141**, 4194.
- 8 A. Saito, Y. Kambara, T. Yagyu, K. Noguchi, A. Yoshimura and V. V. Zhdankin, *Adv. Synth. Catal.*, 2015, **357**, 667.
- 9 L. A. Combee, S. L. Johnson, J. E. Laudenschlager and M. K. Hilinski, *Org. Lett.*, 2019, **21**, 2307.
- 10 For other recent examples of the use of vinylcyclopropanes in N-heterocycle synthesis, see: (a) X.-B. Huang, X.-J. Li, T.-T. Li, B. Chen, W.-D. Chu, L. He and Q.-Z. Liu, *Org. Lett.*, 2019, **21**, 1713; (b) K. Speilmann, E. Tosi, A. Lebrun,



Scheme 3 TEMPO trapping experiment and proposed mechanism for the formation of $[5 + 1]$ products.

- G. Niel, A. van der Lee, R. M. de Figueiredo and J.-M. Campagne, *Tetrahedron*, 2018, **74**, 6497; (c) J. Ling, M. Laugeois, V. Ratovelomanana-Vidal and M. R. Vitale, *Synlett*, 2018, **29**, 2288; (d) Q. Wang, C. Wang, W. Shi, Y. Xiao and H. Guo, *Org. Biomol. Chem.*, 2018, **16**, 4881; (e) C.-H. Liu, F. Li, Y. Yuan, M. Dou and Z.-X. Yu, *Asian J. Org. Chem.*, 2018, **7**, 1609.
- 11 D. A. Evans, M. M. Faul and M. T. Bilodeau, *J. Am. Chem. Soc.*, 1994, **116**, 2742.
- 12 Brief investigations into the effect of ligands (e.g. BOX, PyBOX, etc.) on the Sc-promoted reaction revealed no advantages over the use of Sc(OTf)₃ alone. See the ESI† for details.
- 13 An expanded optimization table including information on the effect of solvents other than CH₂Cl₂ can be found in the ESI.†
- 14 (a) J. J. Verendel, T. Zhou, J.-Q. Li, A. Paptchikhine, O. Lebedev and P. G. Andersson, *J. Am. Chem. Soc.*, 2010, **132**, 8880; (b) K. Meng, J. Xia, Y. Wang, X. Zhang, G. Yang and W. Zhang, *Org. Chem. Front.*, 2017, **4**, 1601.
- 15 (a) G. Dequirez, J. Ciesielski, P. Retailleau and P. Dauban, *Chem. – Eur. J.*, 2014, **20**, 8929; (b) J. Ciesielski, G. Dequirez, P. Retailleau, V. Gandon and P. Dauban, *Chem. – Eur. J.*, 2016, **22**, 9338.
- 16 (a) G. A. Olah, V. P. Reddy and G. K. S. Prakash, *Chem. Rev.*, 1992, **92**, 69; (b) Z. Goldschmidt and B. Crammer, *Chem. Soc. Rev.*, 1988, **17**, 229; (c) W. J. Hehre and P. D. Hiberty, *J. Am. Chem. Soc.*, 1974, **96**, 302; (d) K. B. Wiberg, D. Shobe and G. L. Nelson, *J. Am. Chem. Soc.*, 1993, **115**, 10645; (e) C. D. Poulter and S. Winstein, *J. Am. Chem. Soc.*, 1969, **91**, 3649; (f) C. D. Poulter and S. Winstein, *J. Am. Chem. Soc.*, 1969, **91**, 3650.
- 17 See ESI† for details.
- 18 Alternatively, Sc(OTf)₃ has been shown to catalyze dipolar cycloadditions of styrene-derived aziridines *via* C–N bond cleavage. See: J. S. Yadav, B. V. S. Reddy, S. K. Pandey, P. Srihari and I. Prathap, *Tetrahedron Lett.*, 2001, **42**, 9089.
- 19 (a) T. A. Halgren, J. D. Roberts, J. H. Horner, F. N. Martinez, C. Tronche and M. Newcomb, *J. Am. Chem. Soc.*, 2000, **122**, 2988; (b) M. Newcomb and D. L. Chestney, *J. Am. Chem. Soc.*, 1994, **116**, 9753; (c) M. Newcomb, C. C. Johnson, M. B. Manek and T. R. Varick, *J. Am. Chem. Soc.*, 1992, **114**, 10915; (d) A. L. J. Beckwith and V. W. Bowry, *J. Am. Chem. Soc.*, 1994, **116**, 2710.