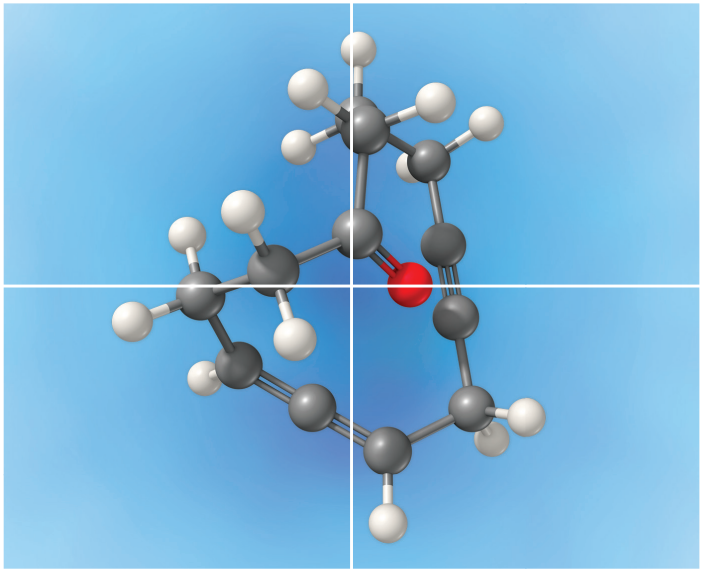
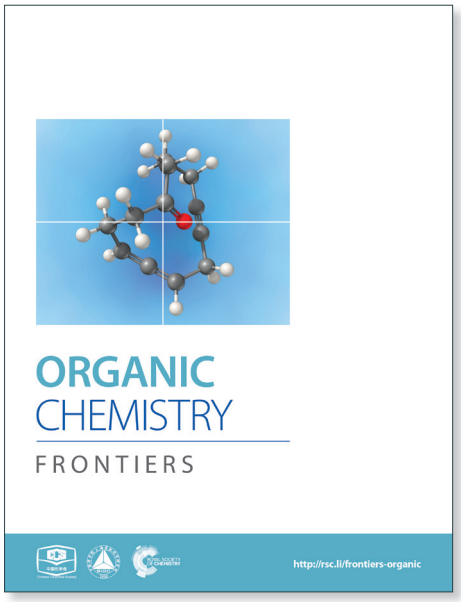
ORGANIC CHEMISTRY

FRONTIERS



Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Organic Chemistry Frontiers

RSCPublishing

HIGHLIGHT

The Redox-A^3 Reaction

Cite this: DOI: 10.1039/xoxxoooooox

Daniel Seidel[a,*]

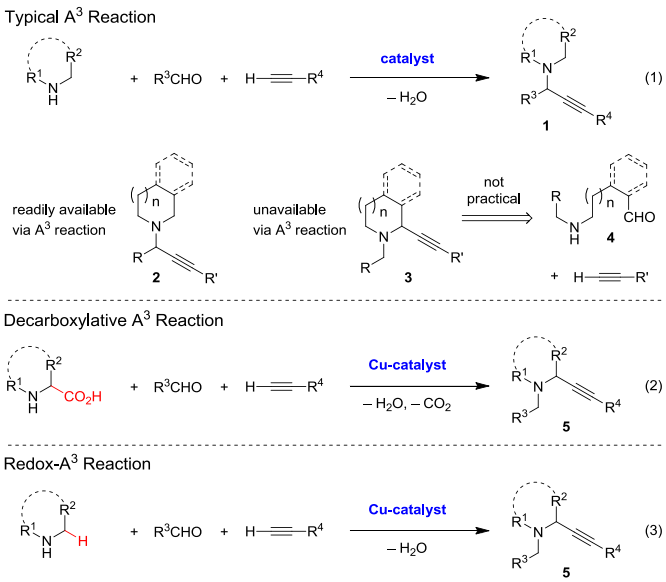
Received ooth January 2014
Accepted ooth January 2014

DOI: 10.1039/xoxxoooooox

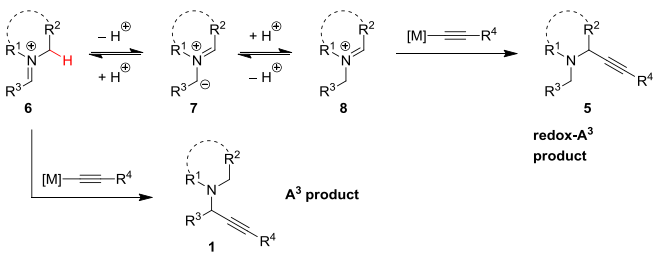
rsc.li/frontiers-organic

This Highlight details the recent emergence of a new type of A^3 reaction (three-component condensation of an amine, an aldehyde and an alkyne). In contrast to the classic A^3 coupling process, the redox-A^3 reaction incorporates an iminium isomerization step and leads to amine α-alkynylation. The overall transformation is redox-neutral by virtue of a combined reductive *N*-alkylation/oxidative C–H bond functionalization.

The three-component coupling of an amine, an aldehyde and an alkyne, commonly known as the A^3 reaction, represents an ideal entry point to synthetically versatile propargylic amines of type **1** (eq 1).[1] Not surprisingly, therefore, a significant amount of attention has focused on this transformation which has resulted in the development of operationally convenient and high-yielding approaches, including enantioselective variants.[1] While cyclic amines readily undergo the A^3 reaction to form propargylic amines with the general structure **2**, the corresponding ring-substituted regioisomers **3** are inaccessible via this method. A two-component alkynylation approach to compounds **3** is not generally feasible due to the difficulties associated with accessing the requisite aminoaldehydes **4**. Here we discuss recent advances that enable the formation of compounds **3** via redox-neutral three-component coupling reactions (eqs 2 & 3).



Previous approaches to ring-substituted propargylic amines related to **3** have focused on the oxidative C–H bond functionalization of tertiary amines (typically *N*-aryl amines and most commonly *N*-aryl tetrahydroisoquinolines).[2] In addition to these transformations which are also referred to as CDC reactions (cross-dehydrogenative coupling reactions),[3] photoredox approaches to amine alkynylation have been reported.[4] The common feature of these two-component strategies is the requirement for an external oxidant. An alternate approach to ring-substituted propargylic amines was developed independently by the Li[5] and Seidel[6] groups.[7,8] These researchers showed that amino acids such as proline and pipecolic acid, when heated with a mixture of an appropriate aldehyde and an alkyne, undergo copper-catalyzed three-component decarboxylative coupling reactions to form propargylic amines **5** (eq 2). The most recent advance in this field, enabling the preparation of ring-substituted propargylic amines, is the redox-A^3 reaction[9–11] which employs the same starting materials as the classic A^3 process (eq 3).[12,13]

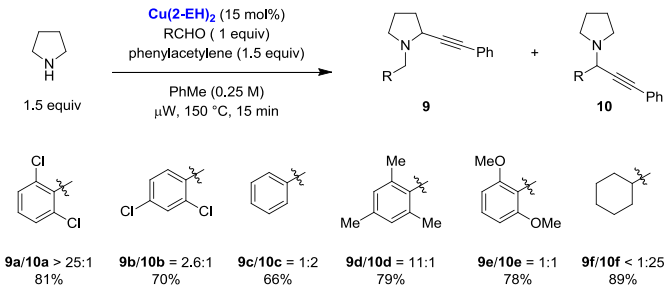


Scheme 1. The A^3 vs. the redox-A^3 reaction, mechanistic considerations.

With regard to the mechanism of the two transformations, both the A^3 reaction and the redox-A^3 reaction likely require the initial formation of iminium ion **6** (Scheme 1). In the classic A^3 process, **6** is trapped with a metal acetylide to give product **1**. In contrast, the redox-A^3 reaction requires the isomerization of iminium ion **6** to its regioisomer **8** which may be achieved via azomethine ylide **7**, an intermediate in the decarboxylative A^3 reaction.[5,6] Through the seminal work of Huisgen and Grigg,[14] it is well established that the deprotonation of iminium ions provides a viable entry to azomethine ylides, species that have been used in various [3+2] and other pericyclic reactions.[15]

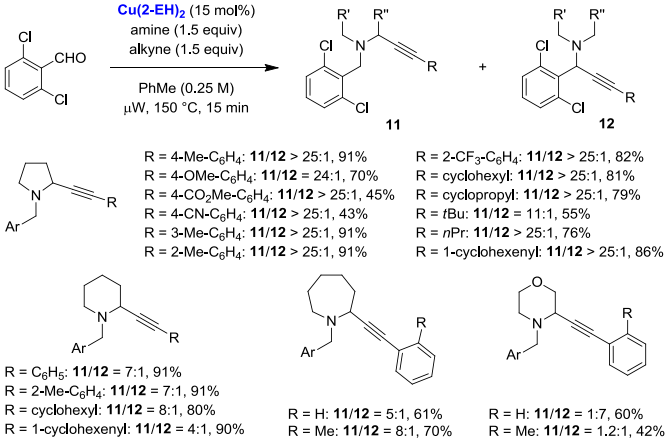
Once formed, protonation of **7** could result in either the original iminium ion **6** or its desired regioisomer **8**. The site of protonation should largely be determined by the charge distribution in **7**, in addition to potential other factors such as sterics. Importantly, evidence has recently been obtained for the intermediacy of azomethine ylides in iminium isomerizations that lead to non-pericyclic amine α-functionalization.[16,17] The realization of a three-component redox-A^3 reaction requires for the iminium isomerization pathway to effectively compete with the direct addition of metal acetylide to **6**. In favorable cases, **5** may be obtained from **1** via stepwise isomerization. This alternate route appears to be viable based on the reversibility of certain iminium alkynylations, as recently demonstrated by Nakamura and co-workers.[18]

The first redox-A^3 reaction was reported by the Seidel group in early 2013.[9] Their strategy was based on the notion that the iminium ion isomerization pathway (*vide supra*) may be accelerated by employing electron-deficient aldehydes. In addition, it was reasoned that sterically demanding aldehydes should slow down the rate of the classic A^3 reaction. 2,6-dichlorobenzaldehyde, an aldehyde that fits these criteria, was evaluated in reactions with pyrrolidine and phenylacetylene. Out of a selection of various commercially available copper(I) and copper(II) compounds, Cu(II) 2-ethylhexanoate (Cu(2-EH)$_2$) was identified as an excellent catalyst. Under the optimized conditions, the redox-A^3 product **9a** was obtained nearly exclusively over the A^3 product **10a** (Scheme 2). The nature of the aldehyde was found to have a dramatic effect on the outcome of the reaction. For instance, electronically similar 2,4-dichlorobenzaldehyde showed only a moderate preference for redox-A^3 product **9b**. In general, for aromatic aldehydes, steric factors appear to outweigh electronics, as illustrated by the observation that mesitaldehyde gave rise to excellent product ratios. However, with aliphatic aldehydes such as cyclohexane-carbaldehyde, the regular A^3 products were obtained almost exclusively. Control experiments showed that limited isomerization of **9a** to **10a** occurs under the reaction conditions, establishing that the product ratios are likely the result of the intrinsic reactivities of the intermediates. Cu(2-EH)$_2$ is thought to play a dual role in the overall process. In addition to forming the copper acetylide, it serves as a source of 2-ethylhexanoic acid which is likely involved in iminium isomerization.



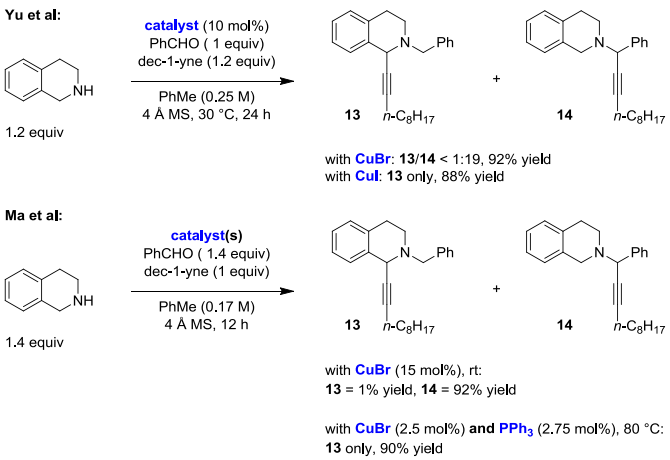
Scheme 2. A^3 vs. redox-A^3 reaction with pyrrolidine: Dependence of product ratios on the aldehyde.

The scope of the Cu(2-EH)$_2$ catalyzed redox-A^3 reaction was evaluated with regard to pyrrolidine and various alkynes (Scheme 3). Good to excellent product ratios and moderate to excellent yields of redox-A^3 products were obtained. Homologues of pyrrolidine were also evaluated and in the case of piperidine and azepane provided synthetically useful product ratios in favor of the redox-A^3 products. Morpholine on the other hand provided mostly regular A^3 product in a reaction with phenylacetylene. Interestingly, replacement of phenylacetylene for *ortho*-tolylacetylene resulted in a slight preference for the redox-A^3 product, illustrating that for a bulkier metal acetylide the rate of the standard A^3 reaction might be slowed down sufficiently to allow for more effective iminium isomerization.



Scheme 3. Scope of the Cu(2-EH)$_2$ catalyzed redox-A^3 reaction by Seidel et al.

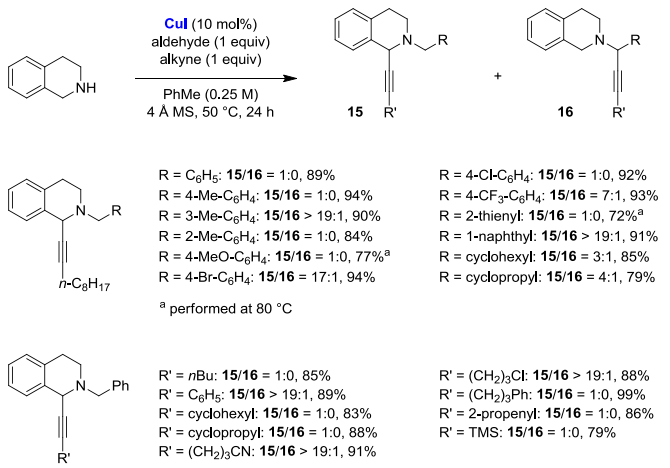
Two independent studies from the Yu[10] and Ma[11] groups, published within a short time frame in late 2013/early 2014, explored the possibility of performing redox-A^3 reactions with tetrahydroisoquinoline (THIQ) as the amine component. Both groups employed the same substrate combination in their initial evaluation of this process (Scheme 4). The two studies showed that reactions of THIQ with benzaldehyde and dec-1-yne, conducted between room temperature and 30 °C in the presence of catalytic amounts of CuBr, resulted in near exclusive formation of the standard A^3 product **14**. Remarkably, Yu et al. found that the simple replacement of CuBr for CuI in a reaction that was conducted under otherwise identical conditions led to the exclusive formation of the redox-A^3 reaction product **13**. The same effect was observed in the Ma study when CuBr was



Scheme 4. Evaluation of catalysts in the redox-A^3 reaction with THIQ.

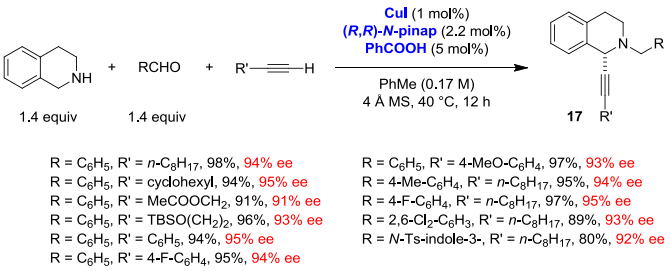
used in combination with triphenylphospine (PPh_3) as a ligand. These authors also noted a dependence of product ratios on

catalyst loading, with lower loadings coupled with higher reaction temperatures giving rise to increased product ratios in favor of the redox-A^3 product **13**. This was rationalized on the basis that lower catalyst loadings should slow down the rate of addition of the copper acetylide to either iminium ion, allowing more time for iminium isomerization. Both studies nicely illustrate the dramatic effect that a counteranion and/or a ligand can exert on the course of an A^3/redox-A^3 reaction.



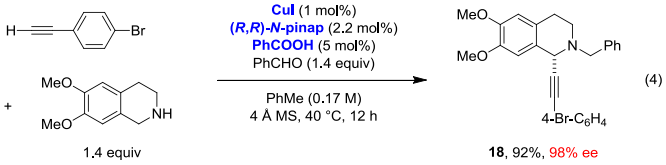
Scheme 5. Scope of the CuI catalyzed redox-A^3 reaction by Yu et al.

The Yu group studied the scope of the redox-A^3 reaction of THIQ with CuI as the catalyst, using a 1:1:1 ratio of substrates (Scheme 5).[10] Excellent results were obtained for a range of different alkynes and aldehydes. In many instances, the redox-A^3 product **15** was formed exclusively over the standard A^3 product **16**. However, a drop in product ratios was observed for aliphatic aldehydes. It was further established that 1,2,3,4-tetrahydro-β-carboline is also amenable to the redox-A^3 reaction (not shown). The authors noted that, under their optimized conditions, pyrrolidine provided exclusively the standard A^3 products.



Scheme 6. Scope of the enantioselective redox-A^3 reaction by Ma et al.

Ma and coworkers, in addition to exploring the scope of the THIQ-based redox-A^3 reaction with the CuBr/PPh$_3$ catalyst system, developed a remarkably efficient enantioselective variant of this process (Scheme 6).[11] A pinap ligand, originally developed by Carreira et al. and used in the regular A^3 reaction,[19] was shown to be ideally suited to facilitate asymmetric redox-A^3 reactions. A low catalyst loading was sufficient and all products were obtained in excellent yields and enantioselectivities. Interestingly, the addition of benzoic acid as a cocatalyst was shown to result in improved yields. The scope of this reaction was further extended to 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, which was shown to undergo a highly enantioselective redox-A^3 reaction (eq 4). Interestingly, Yu et al. reported that under their conditions of CuI catalysis, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline failed to undergo a reaction with benzaldehyde and dec-1-yne; neither A^3 nor redox-A^3 products were isolated.



In conclusion, the recently developed redox-A^3 reaction provides a useful complement to the traditional A^3 coupling process. Ring-substituted propargylic amines not readily available by other means can now be prepared in a single step and in redox-neutral fashion. Some of these reactions proceed under remarkably mild conditions which undoubtedly will encourage their widespread application. The observation that a simple change in counteranion and/or the addition of appropriate ligands can change the course of the reaction from exclusively A^3 to exclusively redox-A^3 bodes well for the development of related redox-transformations.

Acknowledgements

Financial support from the NIH–NIGMS (grant R01GM101389-01) is gratefully acknowledged.

Notes and references

[a] Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, United States.
Email: seidel@rutchem.rutgers.edu

1 Selected reviews on the A^3 reaction: (a) C. Wei, Z. Li and C.-J. Li, *Synlett*, 2004, 1472; (b) L. Zani and C. Bolm, *Chem. Commun.*, 2006, 4263; (c) V. A. Peshkov, O. P. Pereshivko and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2012, **41**, 3790.

2 Selected recent reviews on amine α-functionalization: (a) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel and B. U. W. Maes, *Chem. Eur. J.*, 2012, **18**, 10092; (b) B. Peng and N. Maulide, *Chem. Eur. J.*, 2013, **19**, 13274; (c) Y. Qin, J. Lv and S. Luo, *Tetrahedron Lett.*, 2014, **55**, 551; (d) C. Zheng and S.-L. You, *RSC Adv.*, 2014, **4**, 6173.

3 Selected recent reviews on the CDC reaction: (a) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (b) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem. Int. Ed.*, 2014, **53**, 74.

4 (a) D. B. Freeman, L. Furst, A. G. Condie and C. R. J. Stephenson, *Org. Lett.*, 2012, **14**, 94; (b) M. Rueping, R. M. Koenigs, K. Poscharny, D. C. Fabry, D. Leonori and C. Vila, *Chem. Eur. J.*, 2012, **18**, 5170.

5 H.-P. Bi, Q. Teng, M. Guan, W.-W. Chen, Y.-M. Liang, X. Yao and C.-J. Li, *J. Org. Chem.*, 2010, **75**, 783.

6 C. Zhang and D. Seidel, *J. Am. Chem. Soc.*, 2010, **132**, 1798.

7 For an oxidative/decarboxylative variant, see: H.-P. Bi, L. Zhao, Y.-M. Liang and C.-J. Li, *Angew. Chem. Int. Ed.*, 2009, **48**, 792.

8 Examples of other types of decarboxylative A^3 reactions: (a) H. D. Feng, D. S. Ermolat'ev, G. H. Song and E. V. Van der Eycken, *J. Org. Chem.*, 2011, **76**, 7608; (b) H. D. Feng, D. S. Ermolat'ev, G. H. Song and E. V. Van der Eycken, *Org. Lett.*, 2012, **14**, 1942; (c) H.

Feng, D. S. Ermolat'ev, G. Song and E. V. Van der Eycken, *J. Org. Chem.*, 2012, **77**, 5149.

9 D. Das, A. X. Sun and D. Seidel, *Angew. Chem. Int. Ed.*, 2013, **52**, 3765.

10 Q.-H. Zheng, W. Meng, G.-J. Jiang and Z.-X. Yu, *Org. Lett.*, 2013, **15**, 5928.

11 W. Lin, T. Cao, W. Fan, Y. Han, J. Kuang, H. Luo, B. Miao, X. Tang, Q. Yu, W. Yuan, J. Zhang, C. Zhu and S. Ma, *Angew. Chem. Int. Ed.*, 2014, **53**, 277.

12 For conceptually different α-alkynylations of tertiary amines, see: T. Sugiishi and H. Nakamura, *J. Am. Chem. Soc.*, 2012, **134**, 2504.

13 For Ir-catalyzed α-alkenylations of imines with alkynes, see: S. Sakaguchi, T. Kubo and Y. Ishii, *Angew. Chem. Int. Ed.*, 2001, **40**, 2534.

14 (a) R. Huisgen, R. Grashey and E. Steingruber, *Tetrahedron Lett.*, 1963, 1441; (b) H. Ardill, R. Grigg, V. Sridharan, S. Surendrakumar, S. Thianpatanagul and S. Kanajun, *J. Chem. Soc., Chem. Commun.*, 1986, 602; (c) H. Ardill, X. L. R. Fontaine, R. Grigg, D. Henderson, J. Montgomery, V. Sridharan and S. Surendrakumar, *Tetrahedron*, 1990, **46**, 6449.

15 Selected reviews on azomethine ylides: (a) A. Padwa and W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, Wiley, Chichester, U. K., 2002; (b) C. Najera and J. M. Sansano, *Curr. Org. Chem.*, 2003, **7**, 1105; (c) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765; (d) G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484; (e) T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.*, 2006, 2873; (f) C. Najera and J. M. Sansano, *Top. Heterocycl. Chem.*, 2008, **12**, 117; (g) M. Nyerges, J. Toth and P. W. Groundwater, *Synlett*, 2008, 1269; (h) J. Adrio and J. C. Carretero, *Chem. Commun.*, 2011, **47**, 6784.

16 (a) I. Deb, D. Das and D. Seidel, *Org. Lett.*, 2011, **13**, 812; (b) A. Dieckmann, M. T. Richers, A. Y. Platonova, C. Zhang, D. Seidel and K. N. Houk, *J. Org. Chem.*, 2013, **78**, 4132; (c) M. T. Richers, I. Deb, A. Y. Platonova, C. Zhang and D. Seidel, *Synthesis*, 2013, **45**, 1730.

17 Although mechanistically distinct, the overall isomerization mechanism shares certain features with the biologically important transamination process: (a) S. Mathew and H. Yun, *ACS Catal.*, 2012, **2**, 993. For leading references on recent synthetic applications, see: (b) X. Xiao, Y. Xie, C. Su, M. Liu and Y. Shi, *J. Am. Chem. Soc.*, 2011, **133**, 12914; (c) X. Xiao, M. Liu, C. Rong, F. Xue, S. Li, Y. Xie and Y. Shi, *Org. Lett.*, 2012, **14**, 5270; (d) Y. Wu and L. Deng, *J. Am. Chem. Soc.*, 2012, **134**, 14334; (e) C. Guo, J. Song and L.-Z. Gong, *Org. Lett.*, 2013, **15**, 2676.

18 T. Sugiishi, A. Kimura and H. Nakamura, *J. Am. Chem. Soc.*, 2010, **132**, 5332.

19 T. F. Knoepfel, P. Aschwanden, T. Ichikawa, T. Watanabe and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2004, **43**, 5971.

