RSC Advances

RSC Advances

www.rsc.org/advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances
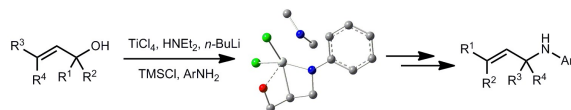
A direct amination on allylic alcohols under mild conditions was enlightened by computational investigations and implemented in secondary allylamines synthesis.

Journal Name

COMMUNICATION

A Computationally Designed Titanium-Mediated Amination of Allylic Alcohols for the Synthesis of Secondary Allylamines

Zunming Sun, Qingxia Wang, Yi Xu, and Zhihong Wang*

 A computational design was inspired by previous mechanistic studies and the DFT-guided reactions were implemented in the synthesis of secondary allylamines. The participation of titanium imido intermediates facilitated the reaction and the closed transition states in the bond-forming steps rendered exclusive S_N2' substitution products.

Computational methods for understanding and promoting chemical reactions have experienced an explosive growth in last several decades. In addition to traditional performance in the rationalization of existing results in chemical processes, computational chemistry has been continually proving its capability to make reliable predictions.[1] In the field of organic chemistry, by delivering instructive information, calculations have played an active part in the development of new catalysts,[2] ligand and molecular design,[3] as well as prediction of reactivity and discovery of new reactions.[4,5] Though, compared with abundant mechanistic studies on existing reactions, reactivity design in advance is still relatively uncommon and only limited examples were timely experimentally verified.[4] Attracted by this emerging subject, we herein report a computationally designed titanium-mediated amination of allylic alcohols for the synthesis of secondary allylamines.

Allylamines, as key building blocks in the transformation to a range of industrially and biologically important products, have been the topic of considerable interest.[6] In comparison with conversions from activated allylic derivatives such as allylic halides, carbonates and carboxylates, direct amination on allylic alcohols possesses an apparent advantage from an economical and environmental point of view, though this scheme is meanwhile challenging due to the poor leaving-group ability of hydroxyl group. The strategy is usually achieved either with the help of precious metal catalysts[7,8] with, in most cases, cooperating activators or unique ligands, or by employing specifically combined catalytic systems.[9]

However, along with the success of converting allylic alcohols

directly into allylamines, these approaches also face some potential problems. Although the regioselectivity can be in principle directed by the choice of catalysts, where platinum and palladium catalysts are inclined to give linear products[7] while iridium and rhodium catalysts favor branched products,[8] elimination of linear products from branched products or vice versa is really difficult since a key step in these catalytic processes is the formation of an η^3-allylic metal complex which is subjected to nucleophilic attack at both ends. In the cases where S_N2 pathway with no involvement of η^3-allylic complex guided the reaction, the regioselectivity is well fixed, but usually at the cost of severe reaction conditions, typically very high temperature.[9a, 9b] A third problem chemists may encounter is the overalkylation which appears when secondary allylamines are desirable.

In an illuminating piece of work, Odom and coworker proposed an effective route to prevent overalkylation in a formal S_N2' substitution reaction using $Ti(NMe_2)_4$ as the mediator, selectively producing secondary allylamines.[10] Though the transfer required strict experimental conditions, typically heating at 160 ºC for hours in a pressure tube. Our previous computational study assigned a [2+2]/retro-[2+2] mechanism to the related reactions while in the titanium-mediated case the high energy requirement of over 43 kcal/mol in the rate-determining [2+2] cycloaddition is supposed to be responsible for the harsh reaction conditions.[11] Grounding on the mechanistic understandings and benefiting from computationally aided reactivity design, we hope to improve this titanium-mediated tactic into a synthetic method for secondary allylamines under general conditions, and at this stage focus on moderating the energy requirement by introducing suitable titanium reaction intermediates into the system (Scheme 1).

Early transition-metal imido complexes are considered to be active participators in the [2+2] cycloadditions[12] and the reactivity is affected by the coordination environment around the central metal, while stronger Lewis acidity of the metal center would favor interaction with electron-donating leaving group in the other cycloaddition partner, namely the allylic alcohol in our desirable reaction and stabilize a closed transition state.[13] In the meantime, the d^0 electron configuration in the Ti(IV) complex could enable partial charge transfer from the π-orbital of the allylic moiety to the empty dz^2-orbital of the central metal, while empty π^*-orbital on the ligands would help to disperse the charge in the transition state as well as intermediate, lowering the energy requirement. From the

State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China
E-mail: zhihongwang@nankai.edu.cn

above two aspects titanium imido halides are qualified candidates for the intermediates in the designed reactions owing to their adequate Lewis acidity, effective coordination to oxygen-containing ligands, and versatile reactivity in cycloadditions.[14] With the help of DFT calculations, we wanted to answer the following questions: to what extent can the involvement of halide ligands reduce the energy requirement; can this reduction realize our vision of converting allylic alcohols and amines directly into allylamines; and from a mechanistic aspect, how would the involvement affect the reaction pathways?
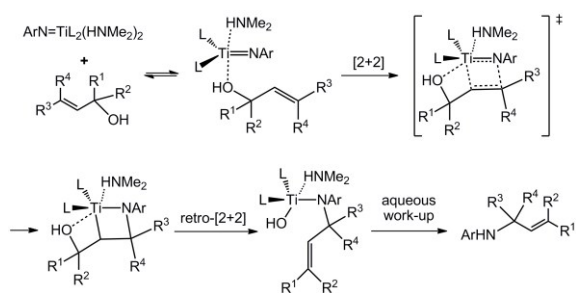
Scheme 1. Designed titanium-mediated amination of allylic alcohols via a formal S_N2' substitution.

As a starting point to this investigation, chloride was selected to exemplify the influence of increased Lewis acidity. Full geometrical optimizations were carried out using Gaussian 09 suite of programs,[15] employing the Minnesota density functional M06.[16] The solvent effect was dealt with using conductor-like polarizable continuum model (CPCM)[17] in toluene. Frequency calculations were performed at the same level to identify all of the stationary points as minima (zero imaginary frequency) or transition states (one imaginary frequency) and intrinsic reaction coordinates (IRC) were calculated for each transition state to confirm that the structure indeed connects the two relevant minima.
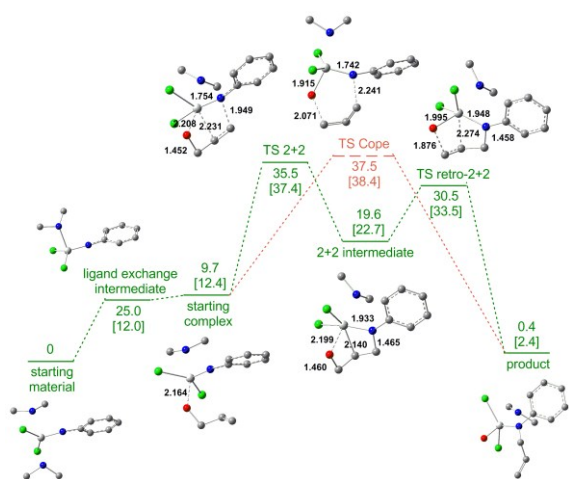
Figure 1. Energy profile and key structures with selected structural parameters (bond lengths in Å) for the reaction of PhN=TiCl₂(HNMe₂)₂. The structures were optimized with M06/6-31++G** method (SDD for Ti) and the solvent effect was dealt with using CPCM (conductor-like polarizable continuum model). The relative electronic energies (with zero-point energies ZPE) are given in kcal/mol and the Gibbs free energy are shown in square brackets.

Compared with the S_N2' substitution using Ti(NMe₂)₄ as the mediator which has an activation energy of 43.1 kcal/mol, the designed amination here incorporating more Lewis acidic PhN=TiCl₂(HNMe₂)₂ as intermediate is proposed to occur at an energy requirement of 35.5 kcal/mol via a [2+2]/retro-[2+2] mechanism with the [2+2] cycloaddition as the rate-determining step (Figure 1).[18] The other mechanistically plausible pathway, namely the [3,3] sigmatropic rearrangement, benefits more from the incorporation of halide ligands, having a remarkably reduced energy (from 59.9 to 37.5 kcal/mol) but still being less energetically favored than the [2+2]/retro-[2+2] mechanism. The dissociation of the product complex is a barrierless process occuring via a transition state which is located 21.4 kcal/mol below the product complex and provides the final product secondary allylamine in an entropy-driven way. Being most important to our design, the energy profile delivered a delightful piece of information that with these energy requirements, the reaction would be able to occur under general conditions like refluxing in commonly-used solvent such as toluene since considering the above-mentioned reaction in literature occurs at 160 ºC in reasonable reaction time, according to Arrhenius equation, to gain a similar reaction rate at 110 ºC, the energy requirement for reaction should be less than 38 kcal/mol (see supporting information for details) while the computationally-predicted barrier of the designed reaction satisfies this demand.

The halide ligands are supposed to facilitate the titanium-mediated amination mainly from two aspects, by increasing the Lewis acidity of the metal center and by dispersing the charge in the transition states. Though not as efficient as chloride in enhancing Lewis acidity, iodide is more polarizable and should have better performance in charge dispersion. Thus parallel calculations were done on the reaction involving PhN=TiI₂(HNMe₂)₂ as intermediate to examine how much can these factors play a role in this particular case (Figure 2).
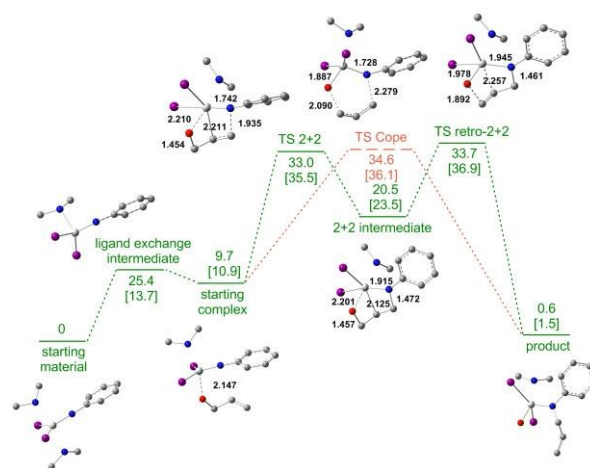
Figure 2. Energy profile and key structures with selected structural parameters (bond lengths in Å) for the reaction of PhN=TiI₂(HNMe₂)₂. The structures were optimized with M06/6-31++G** method (SDD for Ti and I) and the solvent effect was dealt with using CPCM (conductor-like polarizable continuum model). The relative electronic energies (with zero-point energies ZPE) are given in kcal/mol and the Gibbs free energy are shown in square brackets.

Differing from its chloride analog, in the reaction of PhN=TiI₂(HNMe₂)₂, the sigmatropic rearrangement process is slightly energetically favored and a retro-[2+2] ring-opening of the

fused ring intermediate serves as the rate-determining step in the stepwise pathway. The energy difference between the two competing mechanisms is not striking, hence both processes might play a part in the reaction. As a whole the energy requirement in the reaction of PhN=TiI$_2$(HNMe$_2$)$_2$ is further lowered, indicating milder reaction conditions or a faster rate of reaction. An analysis of the computed natural atomic charges along the reaction profiles gave a clue to how the halide ligands facilitated the reaction by increasing the Lewis acidity of the metal center as well as by dispersing charges (Table 1). The calculated charge on the titanium atom in the starting material is markedly increased by the incorporation of chloride as ligand and slightly raised by iodide, supporting our expectation of enhancing the Lewis acidity of the metal center to different degrees. Though not being as effective as chloride in influencing the Lewis acidity, iodide ligand does perform better in dispersing charges, lowering the charge build-up in the transition states as well as the intermediate. As a control system, reaction involving PhN=Ti(NMe2)$_2$(HNMe$_2$)$_2$ experiences greater changes in charge, which might be one of the factors in the obviously higher energy requirement.[18]

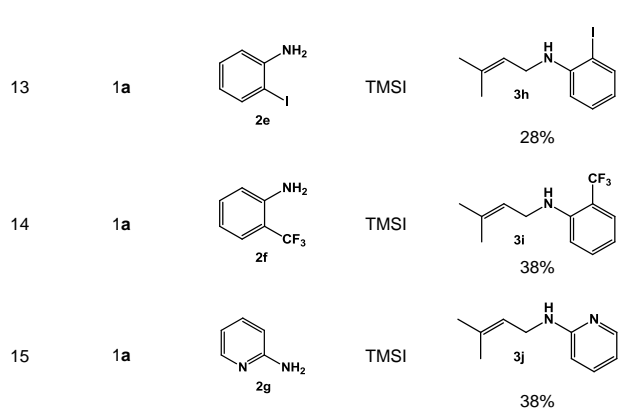**Table 1.** Calculated NBO charges with M06/6-31++G** method (SDD for Ti and I) on the titanium atom.

	PhN=Ti(NMe2)$_2$ (HNMe$_2$)$_2$	PhN=TiCl$_2$(HNMe$_2$)$_2$	PhN=TiI$_2$(HNMe$_2$)$_2$
Starting material	+0.48e	+0.70e	+0.50e
TS 2+2	+0.85e	+0.73e	+0.45e
2+2 intermediate	+0.85e	+0.72e	+0.45e
TS retro-2+2	+0.82e	+0.76e	+0.49e
TS Cope	+1.39e	+0.81e	+0.68e

According to the energy profiles from DFT calculations, the introduction of halide ligands would bring obvious benefit to the realization of synthesis of secondary allylamines from amines and allylic alcohols under relatively mild conditions. To substantiate the concept, we initiated our experimental study by testing the reaction of 2-methylbut-3-en-2-ol with aniline (Table 2, entry 1). To make the reaction further economically and operationally simple, the titanium imido halide intermediates were introduced using inexpensive TiCl$_4$ as metallic reagent and employing trimethylsilyl halides to gain a variety of halide ligands conveniently. Delightfully, the one-pot reaction involving PhN=TiCl$_2$(HNEt$_2$)$_2$ gave exclusively the S$_N$2' product in an acceptable yield in 24 hours with no observation of S$_N$2 product (entry 1), corroborating our original idea to achieve high regioselectivity as the benefit of closed transition states in the key steps. The S$_N$2' selectivity was further confirmed by the reactions of 1**b** and 1**c** (entries 2-3) which usually provided the same product in the reaction involving η^3-allylic complex and yielded different results here, both giving the S$_N$2' product. Comparing with the strict requirements in literature in which heating toluene to 160 ºC in pressure tube and manipulation of reagents in glovebox were indispensable,[10] the experimental conditions here are much gentler. To identify whether the titanium imido chloride intermediates virtually contribute to the reaction and how essential the participation is, control experiments were carried out. Using commercially available Ti(NMe$_2$)$_4$ (entry 4) provided analogous results to that of entry 1, while the absence of trimethylsilyl chloride entirely disabled the reaction (entry 5), supporting the concept that the involvement of titanium imido halide is active and vital.

Table 2. Titanium-mediated amination of allylic alcohols.

Entry	Allylic alcohol 1	Amine 2	TMS halide	Product 3 & Isolated yield (%)
1	1a	PhNH$_2$	TMSCl	3a, 53 %
2	1b	PhNH$_2$	TMSCl	3b, 38 %
3	1c	PhNH$_2$	TMSCl	3c, 24 %
4[a]	1a	PhNH$_2$	TMSCl	3a, 50 %
5	1a	PhNH$_2$	----	----
6	1a	PhNH$_2$	TMSI	3a, 76 %
7	1a	PhNH$_2$	TMSI	3a, 50 % (80 ℃)
8	1c	PhNH$_2$	TMSI	3c, 76 %
9	1d	PhNH$_2$	TMSI	3d, 71 %
10	1a	2b	TMSI	3e, 67 %
11	1a	2c	TMSI	3f, 72 %
12	1a	2d	TMSI	3g, 43 %

13	1a	2e	TMSI	3h 28%
14	1a	2f	TMSI	3i 38%
15	1a	2g	TMSI	3j 38%

[a] Commercially available Ti(NMe$_2$)$_4$ was used instead of that generated in situ.

A primary kinetic study was conducted for the comparison of the proposed mechanism with experimental results. The reaction of 2-methylbut-3-en-2-ol with 4-chloroaniline was selected in the study for the simplification of NMR while corresponding calculation indicated that the substitution led to a tiny change of only 0.1 kcal/mol in the energy requirement. The change in concentration exhibited second-order behavior of bimolecular reactions with identical initial concentration of two starting materials, suggesting a rate constant of 5.5 x 10^{-7} m^{3}mol^{-1}s^{-1} which implied an activation energy of 33.6 kcal/mol according to Eyring-Polanyi equation (Figure 3).
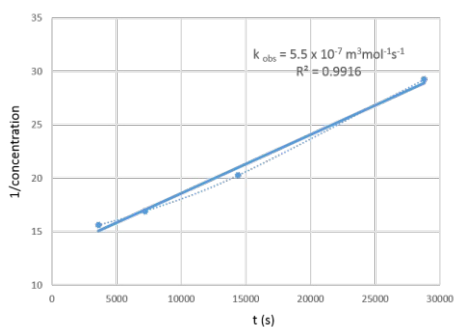
Figure 3. Concentration change of 4-chloroaniline over time and the fitted value of second-order rate constant in the primary kinetic study.

Another mechanistic examination was guided with the consideration that adding substituent on the 2-position of allylic alcohol would make the transition states in the [2+2]/retro-[2+2] pathway more sterically crowded, increase the energy requirement and virtually inhibit the reaction, while the [3,3]-sigmatropic rearrangement or the direct S$_N$2 substitution is much less affected by the steric hindrance on the 2-position, thus the reaction would be appreciably impacted only if the [2+2]/retro-[2+2] pathway serves as the dominant mechanism (Scheme 2). Calculation on the reaction of 2-methylallyl alcohol with PhN=TiCl$_2$(HNMe$_2$)$_2$ specified the energy requirements to be 38.6 and 34.9 kcal/mol for the [2+2] and retro-[2+2] transition states respectively and 38.1 kcal/mol for the sigmatropic rearrangement, adding 3.1 kcal/mol to the barrier of the [2+2]/retro-[2+2] pathway and 0.6 kcal/mol to the sigmatropic rearrangement. The amination product was barely observed in the experiment with high recovery of starting materials and the lack of reactivity practically corroborated our prediction.
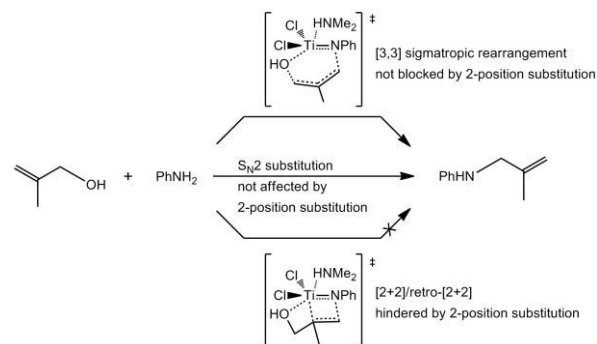
Scheme 2. Potential mechanism and corresponding expected outcomes in the reaction of 2-methylallyl alcohol and aniline.

Encouraged by the results in the reactions mediated by titanium imido chlorides, we turned our attention toward reactions of the iodide analogs that have even lower energy requirement, expecting milder reaction conditions or a faster rate of reaction. To our great delight, one-pot reaction involving PhN=TiI$_2$(HNEt$_2$)$_2$ at reflux in toluene markedly enhanced the isolated yields (76% in entry 6 vs 53% in entry 1, 76% in entry 8 vs 24% in entry 3) while concurrently halved the reaction time. The reaction remained working at further reduced temperature, but at the lower rate (entry 7). Being contrary to the inhibition of reaction by substitution on the 2-position of allylic alcohol, substituents on the 1-position do not impair the effectiveness of the reaction, exclusively providing the S$_N$2' product in satisfactory yield (entries 8-9). While para-substituted anilines provided satisfactory yields (entries 10-12), the efficiency of the reaction was reduced in cases where ortho-functionalized anilines were employed (entries13-14), most probably as the result of steric hindrance at the ortho-position which could be a destabilizing factor in a spatially crowded transition state like the one here for the rate-determining [2+2] cycloaddition step. The suspicion was partially backed up by the fact that in the reaction of 2,6-diisopropylaniline in which the deleterious effect was amplified, only trace amount of product was observed. Aryl amines other than substituted anilines, such as pyridine-2-amine, was also compatible in the direct amination of allylic alcohol, giving S$_N$2' product in a medium yield (entry 15).

Conclusions

In summary, a direct amination on allylic alcohols was enlightened by mechanistic investigations and computationally designed. Titanium imido halides were introduced to facilitate the reaction and realize the regioselective synthesis of secondary allylamines from allylic alcohols and aryl amines without overalkylation. DFT calculations suggested an activation energy of 35.5 kcal/mol in the reaction with the mediation PhN=TiCl$_2$(HNEt$_2$)$_2$ and even lower energy requirement for the reaction involving PhN=TiI$_2$(HNEt$_2$)$_2$. The computationally predicted reactivity was experimentally verified in the one-pot reaction at reflux in toluene, using inexpensive TiCl$_4$ as metallic reagent, gaining agreeable yields and S$_N$2' selectivity under mild conditions. Primary kinetic study suggested an activation energy of 33.6 kcal/mol, basically matching with the computational prediction while the 2-

position substitution on allylic alcohol disabled the reaction, supporting the [2+2]/retro-[2+2] pathway as prevailing mechanism.

Acknowledgements

Notes and references

1   For reviews, see (a) M. Höhne and U. T. Bornscheuer, *Angew. Chem. Int. Ed.* 2014, **53**, 1200-1202; (b) S. Fantacci and F. De Angelis, *Coord. Chem. Rev.* 2011, **255**, 2704-2726; (c) N. M. O'Boyle, C. M. Campbell and G. R. Hutchison, *J. Phys. Chem. C* 2011, **115**, 16200-16210; (d) Z. Lin, *Acc. Chem. Res.* 2010, **43**, 602-611; (e) J. K. Nørskov, T. Bligaard, J. Rossmeisl and C. H. Christensen, *Nat. Chem.* 2009, **1**, 37-46; (f) S. L. Price, *Acc. Chem. Res.* 2009, **42**, 117-126; (g) T. Bligaard, *Angew. Chem. Int. Ed.* 2009, **48**, 9782-9784; (h) K. N. Houk and P. H-Y. Cheong, *Nature* 2008, **455**, 309-313; (i) S.; J. Andrés, V. Moliner, E. Silla, I. Tuñón and J. Bertrán, *Chem. Soc. Rev.* 2008, **37**, 2634-2643..

2   (a) A. Fortunelli, W. A. Goddard, Y. Sha, T. H. Yu, L. Sementa, G. Barcaro and O. Andreussi, *Angew. Chem. Int. Ed.* 2014, **53**, 6669-6672; (b) Y. Sha, T. H. Yu, B. V. Merinov and W. A. III Goddard, *ACS Catal.* 2014, **4**, 1189-1197; (c) X. Du, X. Gao, W. Hu, J. Yu, Z. Luo and K. Cen, *J. Phys. Chem. C* 2014, **118**, 13617-13622; (d) Y. C. Kimmel, L. Yang, T. G. Kelly, S. A. Rykov and J. G. Chen, *J Catal* 2014, **312**, 216-220; (e) E. Larionov, F. Achrainer, J. Humin and H. Zipse, *ChemCatChem* 2012, **4**, 559-566; (f) A. Uhe, M. Hölscher and W. Leitner, *Chem. Eur. J.* 2012, **18**, 170-177; (g) X. Yang, *ACS Catal.* 2011, **1**, 849-854; (h) H. Yang and M. W. Wong, *J. Org. Chem.* 2011, **76**, 7399-7405; (i) L. Zhao, H. Li, G. Lu and Z-X. Wang, *Dalton Trans.* 2010, **39**, 4038-4047; (j) D. J. Tantillo, *Angew. Chem. Int. Ed.* 2009, **48**, 31-32; (k) E. M. Fleming, C. Quigley, I. Rozas and S. J. Connon, *J. Org. Chem.* 2008, **73**, 948-956; (l) J. C. Ianni, V. Anamalai, P. Phuan, M. Panda and M. C. Kozlowski, *Angew. Chem. Int. Ed.* 2006, **45**, 5502-5505; (m) S. Mitsumori, H. Zhang, P. H-Y. Cheong, K. N. Houk, F. Tanaka and C. F. III Barbas, *J. Am. Chem. Soc.* 2006, **128**, 1040-1041.

3   (a) T. O. Lopes, D. A. da Silva Filho, A. A. M. Lapis, H. C. B. de Oliveira and B. A. D. Neto, *J. Phys. Org. Chem.* 2014, **27**, 303-309; (b) V. I. Minkin, A. A. Starikova and R. M. Minyaev, *Dalton Trans.* 2013, **42**, 1726-1734; (c) C. H. Suresh and M. Ajitha, *J. Org. Chem.* 2013, **78**, 3918-3824; (d) S. Schmidt, G. Abkai, T. Rosendahl, F. Rominger and P. Hofmann, *Organometallics* 2013, **32**, 1044-1052; (e) Y. Liang, J. L. Mackey, S. A. Lopez, F. Liu and K. N. Houk, *J. Am. Chem. Soc.* 2012, **134**, 17904-17907.

4   (a) M. C. Nielsen, K.J. Bonney and F. Schoenebeck, *Angew. Chem. Int. Ed.* 2014, **53**, 5903-5906; (b) M. C. Nielsen, E. Lyngvi and F. Schoenebeck, *J. Am. Chem. Soc.* 2013, **135**, 1978-1985; (c) R. Mirabdolbaghi and T. Dudding, *Org. Lett.* 2012, **14**, 3748-3751; (d) F. Proutiere and F. Schoenebeck, *Angew. Chem. Int. Ed.* 2011, **50**, 8192-8195; (e) D. Mulliner, D. Wondrousch and G. Schüürmann, *Org. Biomol. Chem.* 2011, **9**, 8400-8412; (f) Y. Wang, J. Wang, J. Su, F. Huang, L. Jiao, Y. Liang, D. Yang, S. Zhang, P. A. Wender and Z-X. Yu, *J. Am. Chem. Soc.* 2007, **129**, 10060-10061; (g) M. Harmata, P. R. Schreiner, D. R. Lee and P. L. Kirchhoefer, *J. Am. Chem. Soc.* 2004, **126**, 10954-10957.

5   (a) J. Fan, K. An, X. Wang and J. Zhu, *Organometallics* 2013, **32**, 6271-6276; (b) G. Klatt, R. Xu, M. Pernpointner, L. Molinari, T. Q. Hung, F. Rominger, A. S. K. Hashmi and H.

Köppel, *Chem. Eur. J.* 2013, **19**, 3954-3961; (c) S-Y. Tang, J. Shi and Q-X. Guo, *Biomol. Chem.* 2012, **10**, 2673-2682; (d) C. P. Butts, E. Filali, G. C. Lloyd-Jones, P-O. Norrby, D. A. Sale and Y. Schramm, *J. Am. Chem. Soc.* 2009, **131**, 9945-9957.

6   For reviews, see (a) E. M. Skoda, G. C. Davis and P. Wipf, *Org. ProcessRes. Dev.* 2012, **16**, 26-34; (b) M. Jahannsen and K. A. Jørgensen, *Chem. Rev.* 1998, **98**, 1689-1708.

7   (a) S. Sawadjoon and J. S. M. Samec, *Org. Biomol. Chem.* 2011, **9**, 2548-2554; (b) T. Ohshima, Y. Miyamoto, J. Ipposhi, Y. Nakahara, M. Utsunomiya and K. Mashima, *J. Am. Chem. Soc.* 2009, **131**, 14317-14328; (c) G. Mora, O. Piechaczyk, R. Houdard, N. Mézailles, X-F. Le Goff and P. Le Floch, *Chem. Eur. J.* 2008, **14**, 10047-10057; (d) G. Mora, B. Deschamps, S. van Zutphen, X. Le Goff, L. Ricard and P. Le Floch, *Organometallics* 2007, **26**, 1846-1855; (e) M. Utsunomiya, Y. Miyamoto, J. Ipposhi, T. Ohshima and K. Mashima, *Org. Lett.* 2007, **9**, 3371-3374; (f) O. Piechaczyk, C. Thoumazet, Y. Jean and P. Le Floch, *J. Am. Chem. Soc.* 2006, **128**, 14306-14317; (g) C. Thoumazet, H. Grützmacher, B. Deschamps, L. Ricard and P. Le Floch, *Eur. J. Inorg. Chem.* 2006, 3911-3922; (h) Kinoshita, H. Shinokubo and K. Oshima, *Org. Lett.* 2004, **6**, 4085-4088; (i) H. Liang, S. Ito and M. Yoshifuji, *Org. Lett.* 2004, **6**, 425-427; (j) M. Kimura, M. Futamata, K. Shibata and Y. Tamaru, *Chem. Commun.* 2003, 234-235; (k) F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami and M. Yoshifuji, *J. Am. Chem. Soc.* 2002, **124**, 10968-10969.

8   (a) Y. Yamashita, A. Gopalarathnam and J. F. Hartwig, *J. Am. Chem. Soc.* 2007, **129**, 7508-7509; (b) C. Dubs, T. Yamamoto, A. Inagaki and M. Akita, *Chem. Commun.* 2006, 1962-1964.

9   (a) Y. Zhao, S. W. Foo and S. Saito, *Angew. Chem. Int. Ed.* 2011, **50**, 3006-3009; (b) Y. Du, S. Oishi and S. Saito, *Chem. Eur. J.* 2011, **17**, 12262-12267; (c) Y. Tao, B. Wang, B. Wang, L. Qu and J. Qu, *Org. Lett.* 2010, **12**, 2726-2729; (d) Y. Tao, Y. Zhou, J. Qu and M. Hidai, *Tetrahedron Lett.* 2010, **51**, 1982-1984; (e) K. Motokura, N. Nakagiri, K. Mori, T. Mizugaki, K. Ebitani, K. Jitsukawa and K. Kaneda, *Org. Lett.* 2006, **8**, 4617-4620.

10 B. Ramanathan and A. L. Odom, *J. Am. Chem. Soc.* 2006, **128**, 9344-9345.

11 C. Cheng, D. Chen, Z. Wang, *Chem. Eur. J.* 2013, **19**, 120 1208.

12 (a) A. D. Schofield, A. Nova, J. D. Selby, A. D. Schwarz, E. Clot and P. Mountford, *Chem. Eur. J.* 2011, **17**, 265-285; (b) A. D. Schofield, A. Nova, J. D. Selby, C. D. Manley, A. D. Schwarz, E. Clot and P. Mountford, *J. Am. Chem. Soc.* 2010, **132**, 10484-10497; (c) N. Oshi, Y. Nakao, H. Sato and S. Sakaki, *J. Phys. Chem. A* 2010, **114**, 659-665; (d) N. C. Tomson, H. Arnold and R. G. Bergman, *Organometallics* 2010, **29**, 2926-2942; (e) S. Tobisch, *Chem. Eur. J.* 2008, **14**, 8590-8602.

13 G. Lalic, J. L. Krinsky and R. G. Bergman, *J. Am. Chem. Soc.* 2008, **130**, 4459-4465.

14 (a) S. R. Dubberley, A. Friedrich, D. A. Willman, P. Mountford and U. Radius, *Chem. Eur. J.* 2003, 9, 3634-3654; (b) B. D. Ward, A. Maisse-François, P. Mountford and L. H. Gade, *Chem. Commun.* 2004, 704-705; (c) N. Adams, H. R. Bigmore, T. L. Blundell, C. L. Boyd, S. R. Dubberley, A. J. Sealey, A. R. Cowley, M. E. G. Skinner and P. Mountford, *Inorg. Chem.* 2005, **44**, 2882-2894; (d) A. E. Guiducci, C. L. Boyd and P. Mountford, *Organometallics* 2006, **25**, 1167-1187.

15 See supporting information for full citation of Gaussian 09.

16 Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* 2008, **120**, 215-241.

17 M. Cossi, V. Barone, R. Cammi, J. Tomasi, *Chem. Phys. Lett.* 1996, **255**, 327-335.

18 For a better comparison of energy, calculations on the model of PhN=Ti(NMe$_2$)$_2$(HNMe$_2$)$_2$ were done, giving an energy requirement of 40 kcal/mol. See supporting information for details.