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Introduction

The direct breakage of carbon–carbon (C–C) single bonds¹ provides unique opportunities for organic synthesis. Cyclobutane derivatives,^{2,3} especially cyclobutenones,⁴ are privileged synthons because a release of the ring strain *via* carbon–carbon bond breakage can provide versatile reactive intermediates. The thermal four-electron electrocyclic cleavage of cyclobutenones (typically at 100 °C or above) can generate vinyl ketene intermediates that participate in a number of reactions, such as the benzannulation first reported by Danheiser in 1984.⁵ To achieve better reaction control and diversity, transition metal catalysts have been developed to activate cyclobutenones and modulate the subsequent reactions (Scheme 1a).⁴ Typically, the transition metal catalysis process is initiated by oxidative addition of a transition metal catalyst to the C–C bond of cyclobutenones. It has been observed that both chemo- and stereo-selectivities are difficult to control in these otherwise elegant reactions, likely due to the high reactivity of the metal catalyst and the metal-bound intermediates.^{6,7}

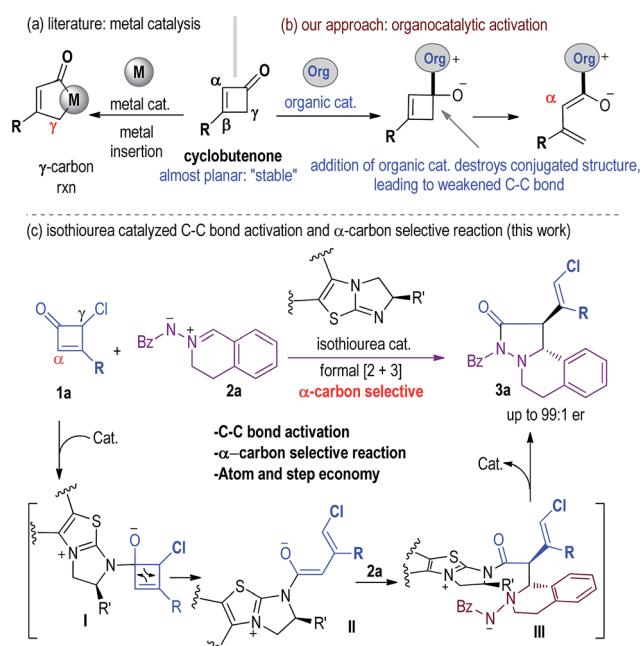
We're interested in using organic catalysts to initiate selective and efficient reactions. It has been observed that the C–C bond of cyclobutenones (and cyclobutenes) can be weakened by

Cycloaddition of cyclobuteneone and azomethine imine enabled by chiral isothiourea organic catalysts†

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The addition of an organic catalyst to the ketone moiety of a γ -mono-chloride substituted cyclobuteneone destroys its stable, conjugated and nearly planar structure. The C–C bond in the resulting less stable anionic oxy-substituted non-planar intermediate is then activated. The breaking of one C–C single bond leads to a catalyst-bound intermediate that undergoes α -carbon selective reactions with azomethine imines to afford nitrogen-containing heterocyclic compounds with excellent diastereo- and enantio-selectivities. Our organocatalytic approach provides a new reaction pattern for C–C bond activation of cyclobuteneones that is unavailable with transition metal catalysis. In addition, the present study with isothioureas as the organocatalysts expands the potential in using organocatalysts for C–C bond breaking and selective reactions.

destroying their nearly planar conjugated structures *via* substitutions, as indicated by computational findings from Houk and co-workers.^{8a,8b} Usually, an “outward” rotation of the thermal electrocyclic ring-opening process is favorable when a substituent is installed at the C4 carbon of cyclobuteneone.⁸ In particular, studies from Baldwin suggested a preference for outward rotation of the chlorine substituent at the C4 carbon of



Scheme 1 Organocatalytic carbon–carbon activation of cyclobuteneones.

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cyclobuteneone.^{8c} By taking advantage of this intrinsic property of cyclobuteneone, we hypothesized that addition of an organic catalyst to the ketone moiety of cyclobuteneone might achieve the activation of the carbon–carbon single bond *via* formation of a non-planar intermediate that leads to the breakage of its C–C bond for further reactions (Scheme 1b).⁹ This reaction would constitute a highly efficient approach in organocatalysis, in which all atoms of the substrate end up in the product (atom economy) and no overall redox process is involved (redox economy). Recently, we reported the addition of an N-heterocyclic carbene catalyst to the ketone moiety of cyclobutenes to initiate highly enantioselective formal [4 + 2] reactions, in which the γ -carbon of cyclobuteneone reacted as a nucleophilic carbon.⁹ Here, we report highly selective [3 + 2] reactions by using an isothiourea organic catalyst to activate and modulate the reactivities/selectivities of mono-chloride substituted cyclobutenones (Scheme 1c).

Results and discussion

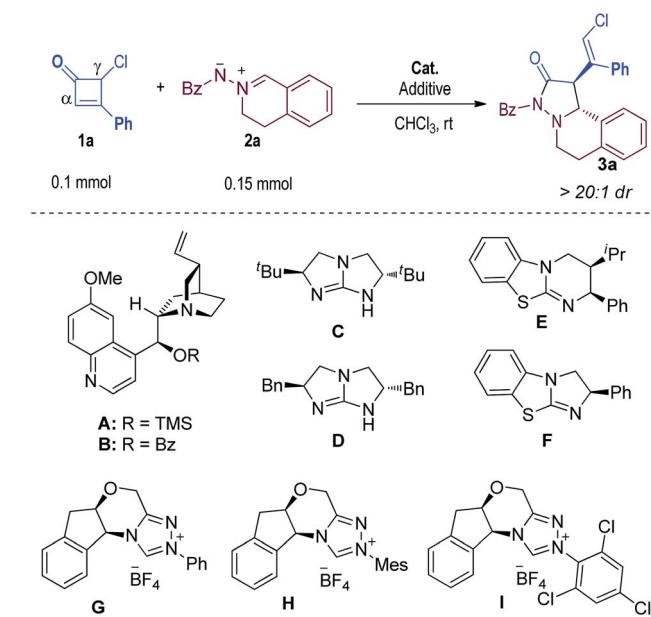
Under the catalysis of isothiourea with cyclobutene **1a** and azomethine imine¹⁰ **2a** as the substrate, the reaction exclusively took place on the α -carbon of the cyclobutene *via* a formal [2 + 3] process. Our result is consistent with an earlier report by Smith that the reaction of the isothiourea-generated dienolate intermediate is α -carbon selective.^{12e} Notably, Studer has recently reported the [2 + 3] cycloaddition of azomethine imines with enolates prepared using an isothiourea catalyst.^{10d} Briefly, in our reaction, nucleophilic 1,2-addition of the isothiourea catalyst to the ketone moiety of cyclobutene **1a** generates intermediate **I** (the conjugated structure is broken and an anionic oxy-substituted intermediate **I** is formed) that undergoes subsequent C-C bond cleavage to form intermediate **II**. The anionic oxy-substituent of **I** likely accelerates the electrocyclic ring opening process.^{8d} The α -carbon of the vinyl enolate^{11,12} selectively reacts with azomethine imine **2a** to form product **3a** with excellent enantioselectivity and diastereoselectivity. The intermediate **II** likely adopts an *s-cis* diene configuration, and the *cis*-configuration of Cl and Ph substituents on the γ - and β -carbon of our product **3a** suggests that intermediate **II** adopts an “outward” configuration.⁸ Previous studies from Houk and Baldwin have suggested that the ring-opening of cyclobutene led to an intermediate similar to **II** with an “outward” configuration.⁸ It is noteworthy that isothiourea as a Lewis base catalyst has not been exploited for the activation of cycloketones.

We started by using cyclobutenone **1a** and azomethine imine **2a** as the model substrates (Table 1). We first examined cinchona alkaloid nucleophilic catalysts and found that no product was obtained with either **A** or **B** as the catalysts (entries 1 and 2).¹³ We next evaluated chiral guanidines, organocatalysts previously explored by Corey,¹⁴ Tan¹⁵ and others.¹⁶ We were delighted to find that the proposed product **3a** could be formed in moderate yields (entries 3 and 4), although attempts to obtain enantioselectivity using guanidine catalysts were unsuccessful. Encouraged by these results, we subsequently studied isothioureas, analogs of guanidines, as the organic catalysts. Notably, pioneering studies in using isothioureas as enantioselective organic

catalysts have been reported by Birman,¹⁷ Smith¹⁸ and others.^{19,20} Here, we found that when isothiourea **E**¹⁷ was used as the catalyst with CHCl_3 as the solvent at room temperature, **3a** could be obtained in 62% yield and with a promising 85 : 15 er (entry 5). The use of catalyst **F**¹⁷ led to **3a** in similar yield with improved er (96 : 4) under otherwise identical conditions (entry 6). Finally, we found that the use of Et_3N as an additive could slightly (and consistently) improve the enantioselectivity (97 : 3) and yield (67%) (entry 7). Decreasing the catalyst loading to 10 mol% gave the product **3a** in lower yield (38%) without an apparent change in enantioselectivity (entry 7). Finally, we compared NHC catalysts that were used in our earlier [4 + 2] reactions (entries 8–10).⁹ These carbene catalysts could lead to products in low yields but with nearly no enantioselectivity.

With acceptable conditions in hand, we next evaluated the scope of the asymmetric reaction by first varying the substituents at the β -carbon of cyclobuteneone substrate **1** (Table 2, **3a-f**).

Table 1 Optimization of the reaction conditions^a

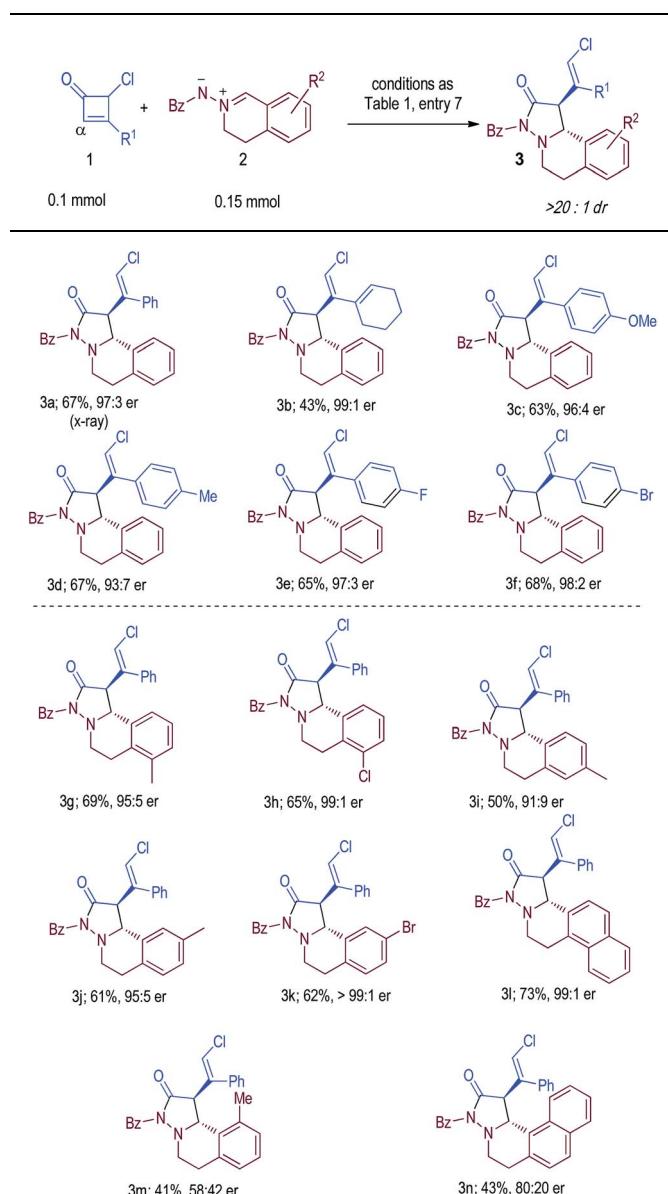


Entry	Cat.	Additive	3a yield ^c (%)	3a ^e er
1	A	—	0	—
2	B	—	0	—
3	C	—	48	50 : 50
4	D	—	38	50 : 50
5	E	—	62	85 : 15
6	F	—	65	96 : 4
7	F	Et ₃ N ^b	67 (38) ^d	97 : 3
8	G	Cs ₂ CO ₃	35	50 : 50
9	H	Cs ₂ CO ₃	40	52 : 46
10	I	Cs ₂ CO ₃	42	52 : 46

^a All reactions of **1a** (0.10 mmol, 17.8 mg) with **2a** (0.15 mmol, 38 mg) were carried out in the presence of catalyst (20 mol%; 20 mol% Cs_2CO_3 was added for **G-I**) in CHCl_3 (1.0 mL) for 3 days. ^b Et_3N (1.0 mmol, 14.0 μL) was added. ^c Isolated yield. ^d F (10 mol%) was used. ^e er of **3a** was determined by chiral HPLC analysis.

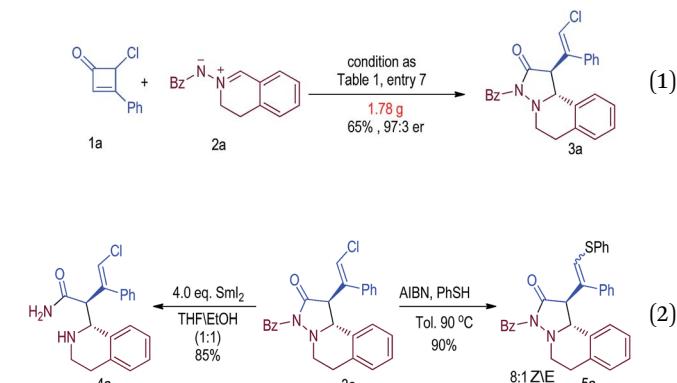
Replacing the Ph substituent in **1a** with an alkyl unit could give the desired product **3b** with excellent enantioselectivity, albeit with a lower yield. Electron-donating and withdrawing substituents on the Ph group of **1a** were also well tolerated, giving products **3c-f** in good yields and excellent enantioselectivities. Azomethine imine substrates were then examined (**3g-n**). It appeared that sterically hindered substrates (**3m, 3n**) led to lower yields and er values under the current reaction conditions. The absolute configurations of the products were confirmed *via* X-ray diffraction of product **3a**.²¹

Notably, when the chlorine atom of substrate **1** was changed to a proton substituent or when γ,γ' -di-chloride substituted

Table 2 Reaction scope^a

^a Conditions as Table 1 entry 7 unless otherwise specified, dr of products were determined *via* ¹H NMR analysis, isolated yields after column chromatography.

cyclobuteneone was used, no cycloaddition products were obtained under our reaction conditions. In these cases, the cyclobuteneone substrates remained unreacted. These results are consistent with Houk's computational findings that cyclobuteneones bearing a mono-substituent at the C4 position are more reactive (less stable). When the chlorine atom of substrate **1** was changed to a methyl substituent, the methyl substituted substrate was unreactive under our catalytic conditions. It appears that with a methyl substituent the ketone moiety is not reactive enough (likely due to electronic reasons). This result is different from our early NHC-catalyzed reactions,⁹ likely because isothiourea organic catalysts are less nucleophilic than NHC catalysts.²²



The catalytic reaction can be carried out on a gram scale without loss of yield and selectivity (eqn (1)).²³ As a technical note, the catalyst (**F**) could be recovered (*via* SiO_2 column chromatography) and reused without loss of reaction efficiency and selectivity. The catalytic product **3a** from our reaction could readily undergo further transformations to give nitrogen-containing heterocyclic compounds (eqn (2)).²⁴ For example, the N-N bond in **3a** could be cleaved in the presence of SmI_2 with ethanol as the solvent to give product **4a**. The vinyl chloride unit in **3a** is a widely used functional group in organic synthesis. Here, we show that the chloride atom in **3a** can be substituted by a sulfa substituent to give product **5a**.

Conclusions

In summary, we have developed a new C-C bond activation of cyclobuteneones enabled by an isothiourea organocatalyst. The catalytically generated intermediate undergoes an α -carbon selective reaction with azomethine imines to afford nitrogen-containing heterocyclic compounds with excellent diastereo- and enantio-selectivities. Our approach offers new reaction modes that are not readily available with transition metal catalysis. It also expands the potential in using organocatalysts for C-C bond breaking and selective reactions.

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Notes and references

- For reviews on C–C bond activation: (a) R. H. Crabtree, *Chem. Rev.*, 1985, **85**, 245; (b) B. Rybchinski and D. Milstein, *Angew. Chem., Int. Ed.*, 1999, **38**, 870; (c) M. E. van der Boom and D. Milstein, *Chem. Rev.*, 2003, **103**, 1759; (d) C.-H. Jun, *Chem. Soc. Rev.*, 2004, **33**, 610; (e) D. Nečas and M. Kotora, *Curr. Org. Chem.*, 2007, **11**, 1566; (f) M. Tobisub and N. Chatani, *Chem. Soc. Rev.*, 2008, **37**, 300; (g) C. Aïssa, *Synthesis*, 2011, **21**, 3389; (h) T. Seiser, T. Saget, D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2011, **50**, 7740.
- Recent selected reviews: (a) J. C. Namyslo and D. E. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485; (b) T. J. Snape, *Chem. Soc. Rev.*, 2007, **36**, 1823; (c) K. Prantl and J. Mulzer, *Chem. Rev.*, 2010, **110**, 3741; (d) E. Leemans, M. D'hooghe and N. de Kimpe, *Chem. Rev.*, 2011, **111**, 3268; (e) Z.-L. Song, C.-A. Fan and Y.-Q. Tu, *Chem. Rev.*, 2011, **111**, 7523.
- For reactions involving ring-opening of cyclobutane alcohol: (a) T. Nishimura and S. Uemura, *J. Am. Chem. Soc.*, 1999, **121**, 11010; (b) B. M. Trost and T. Yasukata, *J. Am. Chem. Soc.*, 2001, **123**, 7162; (c) T. Seiser and N. Cramer, *Angew. Chem., Int. Ed.*, 2008, **47**, 9294; (d) E. Zhang, C.-A. Fan, Y.-Q. Tu, F.-M. Zhang and Y.-L. Song, *J. Am. Chem. Soc.*, 2009, **131**, 14626.
- (a) D. Bellus and B. Ernsts, *Angew. Chem., Int. Ed.*, 1988, **27**, 797; (b) T. Xu and G. Dong, *Angew. Chem., Int. Ed.*, 2012, **51**, 7567; (c) P.-H. Chen, T. Xu and G. Dong, *Angew. Chem., Int. Ed.*, 2014, **53**, 1674; (d) A. Cammers-Goodwi, *J. Org. Chem.*, 1993, **58**, 7619; (e) M. Murakami, Y. Miyamoto and Y. Ito, *J. Am. Chem. Soc.*, 2001, **123**, 6441; (f) N. A. Magomedov, P. L. Ruggiero and Y. Tang, *J. Am. Chem. Soc.*, 2004, **126**, 1624.
- (a) R. L. Danheiser and S. K. Gee, *J. Org. Chem.*, 1984, **49**, 1672; (b) S. T. Perri, L. D. Foland, O. H. W. Decker and H. W. Moore, *J. Org. Chem.*, 1986, **51**, 3067; (c) X. Y. Mak, A. L. Crombie and R. L. Danheiser, *J. Org. Chem.*, 2011, **76**, 1852.
- For asymmetric C–C activation under metal-catalysis: (a) T. Matsuda, M. Shigeno and M. Murakami, *J. Am. Chem. Soc.*, 2007, **129**, 12086; (b) C. Nájera and J. M. Sansano, *Angew. Chem., Int. Ed.*, 2009, **48**, 2452; (c) C. Winter and N. Krause, *Angew. Chem., Int. Ed.*, 2009, **48**, 2460; (d) T. Seiser and N. Cramer, *Org. Biomol. Chem.*, 2009, **7**, 2835; (e) T. Xu, H. M. Ko, N. A. Savage and G. Dong, *J. Am. Chem. Soc.*, 2012, **134**, 20005; (f) T. Seiser and N. Cramer, *Chem.–Eur. J.*, 2010, **16**, 3383; (g) L. Souillart, E. Parker and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 3001.
- H. M. Ko and G. Dong, *Nat. Chem.*, 2014, **6**, 789.
- (a) S. E. Niwayama, A. Kallel, C. Sheu and K. N. Houk, *J. Org. Chem.*, 1996, **61**, 2517; (b) W. Kirmse, N. G. Rondan and K. N. Houk, *J. Am. Chem. Soc.*, 1984, **106**, 7989; (c) J. E. Baldwin and M. C. McDanie, *J. Am. Chem. Soc.*, 1968, **90**, 6118; (d) M. Murakami, Y. Miyamoto and Y. Ito, *J. Synth. Org. Chem., Jpn.*, 2002, **60**, 1049.
- (a) B.-S. Li, Y. Wang, Z. Jin, P. Zheng, R. Ganguly and Y. R. Chi, *Nat. Commun.*, 2015, **6**, 6027.
- For related organocatalytic asymmetric [3 + 2] cycloaddition reactions: (a) T. Hashimoto, Y. Maeda, M. Omote, H. Nakatsu and K. Maruoka, *J. Am. Chem. Soc.*, 2010, **132**, 4076; (b) T. Hashimoto, M. Omote and K. Maruoka, *Angew. Chem., Int. Ed.*, 2011, **50**, 3489; (c) T. Hashimoto, M. Omote and K. Maruoka, *Angew. Chem., Int. Ed.*, 2011, **50**, 8952; (d) L. Hesping, A. Biswas, C. G. Daniliuc, C. Mück-Lichtenfeld and A. Studer, *Chem. Sci.*, 2015, **6**, 1252.
- For γ -activation of NHC catalysis, see: (a) H. U. Vora, P. Wheeler and T. Rovis, *Adv. Synth. Catal.*, 2012, **354**, 1617; (b) J. Mo, X. Chen and Y. R. Chi, *J. Am. Chem. Soc.*, 2012, **134**, 8810; (c) X. Chen, S. Yang, B.-A. Song and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2013, **52**, 11134; (d) Y.-M. Zhao, M. S. Cheung, Z. Lin and J. Sun, *Angew. Chem., Int. Ed.*, 2012, **51**, 10359; (e) X.-Y. Chen, F. Xia, J.-T. Cheng and S. Ye, *Angew. Chem., Int. Ed.*, 2013, **52**, 10644.
- For vinyl enolate generated from ammonium intermediate, see: (a) P. S. Tiseni and R. Peters, *Angew. Chem., Int. Ed.*, 2007, **46**, 5325; (b) P. S. Tiseni and R. Peters, *Org. Lett.*, 2008, **10**, 2019; (c) L. Shen, P. Shao and S. Ye, *Adv. Synth. Catal.*, 2011, **353**, 1943; (d) L. Shen, L. Sun and S. Ye, *J. Am. Chem. Soc.*, 2011, **133**, 15894; (e) L. C. Morrill, S. M. Smith, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.*, 2014, **79**, 1640. For recent review of covalent bond catalysis, see: (f) M. C. Holland and R. Gilmour, *Angew. Chem., Int. Ed.*, 2015, **54**, 3862.
- (a) M. A. Calter, *J. Org. Chem.*, 1996, **61**, 8006; (b) S. Vellalath, K. N. van and D. Romo, *Angew. Chem., Int. Ed.*, 2013, **52**, 13688.
- E. J. Corey and M. J. Grogan, *Org. Lett.*, 1999, **1**, 157.
- (a) W. Ye, D. Leow, S. L. M. Goh, C.-T. Tan, C.-H. Chian and C.-H. Tan, *Tetrahedron Lett.*, 2006, **47**, 1007; (b) J. Wang, J. Chen, C. W. Kee and C.-H. Tan, *Angew. Chem., Int. Ed.*, 2012, **51**, 2382.
- (a) M. Terada, M. Nakano and H. Ube, *J. Am. Chem. Soc.*, 2006, **128**, 16044; (b) M. Terada, M. Nakano and H. Ube, *J. Am. Chem. Soc.*, 2007, **129**, 14112; (c) T. Misaki, K. Kawano and T. Sugimura, *J. Am. Chem. Soc.*, 2011, **133**, 5695.
- V. B. Birman and X. Li, *Org. Lett.*, 2006, **8**, 1351.
- (a) C. Joannes, C. P. Johnston, C. Concellón, C. Simal, D. Philp and A. D. Smith, *Angew. Chem., Int. Ed.*, 2009, **48**, 8914; (b) L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox and A. D. Smith, *Chem. Sci.*, 2013, **4**, 4146; (c) E. R. T. Robinson, C. Fallan, C. Simal, A. M. Z. Slawin and A. D. Smith, *Chem. Sci.*, 2013, **4**, 2193; (d) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc.*, 2011, **133**, 2710.
- (a) M. S. Kerr, J. Read de Alaniz and T. Rovis, *J. Org. Chem.*, 2005, **70**, 5725; (b) M. He, J. R. Struble and J. W. Bode, *J. Am. Chem. Soc.*, 2006, **128**, 8418; (c) H. U. Vora and T. Rovis, *J. Am. Chem. Soc.*, 2007, **129**, 13796; (d)



H. U. Vora, J. R. Moncecchi, O. Epstein and T. Rovis, *J. Org. Chem.*, 2008, **73**, 9727.

20 (a) G. Liu, M. E. Shirley, K. N. van, R. L. McFarlin and D. Romo, *Nat. Chem.*, 2013, **5**, 1049; (b) R. W. T. Clark, M. Deaton, Y. Zhang, M. Moore and S. L. Wiskur, *Org. Lett.*, 2013, **15**, 6132.

21 ESI†

22 (a) L. Candish, Y. Nakano and D. W. Lupton, *Synthesis*, 2014, **46**, 1823; (b) B. Maji, C. Joannesse, T. A. Nigst, A. D. Smith and H. Mayr, *J. Org. Chem.*, 2011, **76**, 5104; (c) B. Maji, M. Breugst and H. Mayr, *Angew. Chem., Int. Ed.*, 2011, **50**, 6915; (d) H. Mayr, S. Lakhdar, B. Maji and A. R. Oflal, *Beilstein J. Org. Chem.*, 2012, **8**, 1458.

23 ESI†

24 (a) W. A. Gallimore and P. J. Scheuer, *J. Nat. Prod.*, 2000, **63**, 1422; (b) K. E. Milligan, B. Márquez, R. T. Williamson, M. Davies-Coleman and W. H. Gerwick, *J. Nat. Prod.*, 2000, **63**, 965; (c) S. Suntornchaswej, K. Suwanborirux, K. Koga and M. Isobe, *Chem.-Asian J.*, 2007, **2**, 114; (d) K. L. Malloy, T. L. Suyama, N. Engene, H. Debonsi, Z. Cao, T. Matainaho, C. Spadafora, T. F. Murray and W. H. Gerwick, *J. Nat. Prod.*, 2012, **75**, 60.

