Ring-Rearrangement Metathesis of Substituted 2-Aminonorbornenes

Adam E. Nadany, John E. Mckendrick*

Department of Chemistry, University of Reading, Whiteknights, Reading, RG6 6AD, UK
Fax +44(118)3786331; E-mail: j.e.mckendrick@reading.ac.uk

Received 3 April 2007

Abstract: In this report we describe the ring-rearrangement metathesis of 2-aminonorbornene derivatives. An efficient ruthenium-catalysed metathesis reaction occurs with a wide range of pendent alkenes and alkynes to generate bicyclic amines and amides.

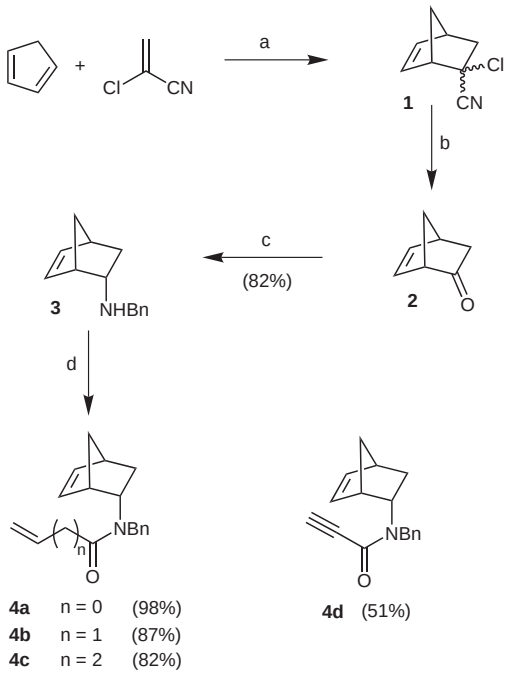
Key words: metathesis, Diels–Alder reaction, piperidine alkaloids

Olefin metathesis has now become an established synthetic tool in organic synthesis. The introduction of Schrock's catalyst,[1] and the widely used Grubbs and Hoveyda catalysts,[2,3] have resulted, not only in a number of alkene formation processes including: ring-closing metathesis (RCM),[4] ring-opening metathesis (ROM), and cross-metathesis (CM),[5] but also the development of a number of 'domino' processes utilising combinations of these basic metathesis processes to prepare complex molecules.[6]

Domino metathesis or ring-rearrangement metathesis (RRM) reactions result in products with rearranged cyclic skeleton. These result from an intramolecular metathesis reaction between an endocyclic olefin and a tethered exocyclic C=C double bond, in such a way that one ring is opened in a ROM process and subsequently a new ring is formed in a RCM process.[7] Ring-rearrangement metathesis has the potential to lead to complex polycycles in a stereocontrolled manner; any stereochemistry present in the starting material is conserved during the reaction and preserved in the reaction products.

Ring-rearrangement metathesis has been previously used to prepare molecules with carbocyclic and oxocyclic frameworks,[8–10] but there have been fewer reports on the application of this reaction to systems containing other heteroatoms such as nitrogen.[11,12]

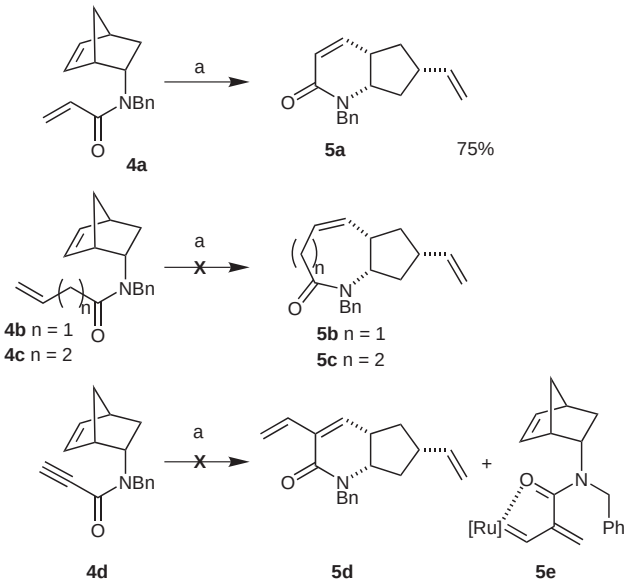
Reported herein are our initial results exploring the synthetic potential of the 2-aminonorbornene system as a suitable substrate core for RRM. Norbornene **1** was prepared through a two-step, one-pot procedure that began with the cycloaddition of cyclopentadiene and 2-chloroacrylonitrile.[13] The Diels–Alder adduct was then treated with potassium hydroxide in DMSO to convert the α-chloronitrile into the desired ketone **2** (Scheme 1). Subsequent reductive amination of **2** using benzylamine in the presence of sodium triacetoxyborohydride, resulted in *N*-benzyl-2-aminonorbornene (**3**).[14] Acylation of *N*-benzyl-2-aminonorbornene (**3**) with acryloyl chloride, but-3-enoyl chloride or pent-4-enoyl chloride in the presence of DMAP gave amides **4a**–**c** in good yield.



Scheme 1 *Reagents and conditions*: (a) toluene, 70 °C, then 45 °C, 18 h; (b) KOH, DMSO, H_2O, 48 h r.t.; (c) benzylamine, AcOH, THF, $NaHB(OAc)_3$; (d) for **4a**–**c**: $H_2C{=}CH(CH_2)_nCOCl$, DMAP, CH_2Cl_2; **4d**: $HC{\equiv}CCO_2H$, DCC, DMAP, CH_2Cl_2.

Metathesis of the vinyl amide **4a** with the Grubbs II catalyst under an atmosphere of ethene resulted in an efficient conversion (75%) to bicyclic amide **5a** (Scheme 2).[15] Encouraged by this result, metathesis of the higher homologues **4b** and **4c** using identical conditions resulted in recovery of only starting norbornenes **4b** and **4c**. Presumably, the reaction had been shut down through sequestration of the catalyst, chelation of the ruthenium to the carbonyl oxygen of the amide would result in a five- or six-membered ring. Precoordination of the aminonorbornenes **4b** and **4c** with a Lewis acid (TiO^iPr_4), following the procedure developed by Fürstner, and subsequent treatment with Grubbs I catalyst resulted in destruction of the starting material in our hands.[16] Acylation of **3** with propiolic acid in the presence of DCC and DMAP gave **4d**. Metathesis of **4d** using the second generation Grubbs catalyst resulted in the recovery of aproximately 90% of the starting material, the mass balance of the reaction was thought to be consumed into an unproductive ruthenium complex of the type **5e**.[17]

SYNLETT 2007, No. 11, pp 1663–1666
Advanced online publication: 25.06.2007
DOI: 10.1055/s-2007-982573; Art ID: G12407ST

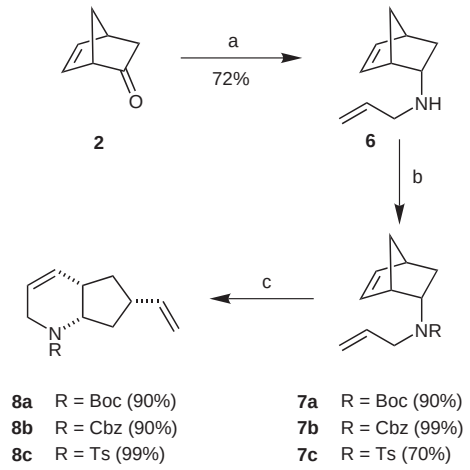


Scheme 2 *Reagents and conditions*: (a) Grubbs II (10 mol%), ethene, CH_2Cl_2.

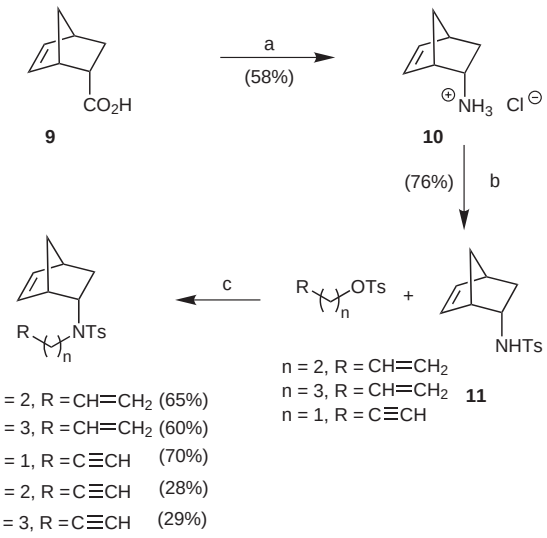
In order to circumvent the problems of catalyst coordination to an amide carbonyl we chose to undertake further study of the RRM reaction with analogous amine substrates. Therefore, reductive amination of **2** using allylamine and sodium triacetoxyborohydride, resulted in *N*-allyl-2-aminonorbornene (**6**, Scheme 3).[14] Protection of the amine prior to the RRM reaction was undertaken and the facile introduction of protecting groups, Boc, Cbz and Ts, gave three substrates on which to test the metathesis reaction. Treatment of the protected *N*-allyl-2-aminonorbornenes **7a**–**c**, with the first generation Grubbs catalyst, under an atmosphere of ethene, resulted in efficient conversion into the desired bicyclic amines **8a**–**c**.[18] All of the protecting groups were facile to install, however, the Ts group provided the opportunity to exploit the enhanced acidity of the NH proton in other synthetic routes and for this reason it was chosen as the standard amine protecting group.

As the preparation of the 5,6-fused bicycle had proven to be straightforward, attention turned to the possibility of preparing other bicyclic amines with larger heterocyclic rings. Problems arising from the instability of longer-chain unsaturated aldehydes prevented synthesis via the reductive amination route. Consequently, Curtius rearrangement of norbornene **9**, derived from Diels–Alder reaction of cyclopentadiene and acryloyl chloride, gave 2-aminonorbornene hydrochloride **10** (Scheme 4).[11h,19] Protection and activation of the amine as its *p*-toluenesulfonate resulted in **11**; alkylation of the anion of **11**, formed by deprotonation using sodium hydride, with alkenol toluenesulfonates gave five metathesis substrates **12a**–**e**.

Rearrangement of aminonorbornenes **12a**–**d** with Grubbs I catalyst (ethene atmosphere) resulted in clean conversion in good yields to the corresponding 5,7- and 5,8-fused bicyclic amines **13a** and **13b** and the vinyl-substituted 5,6- and 5,7-fused bicycles **13c** and **13d**, resulting from an efficient ene–yne metathesis reaction (Scheme 5). Disappointingly, RRM of aminonorbornene **12e** resulted in only the ring-opened structure **13e**, no evidence of any ring-closed ene–yne reaction was evident from the NMR spectrum. That the yields were lower, but acceptable, is a reflection of the increase in ring size formed upon ring-closing metathesis.

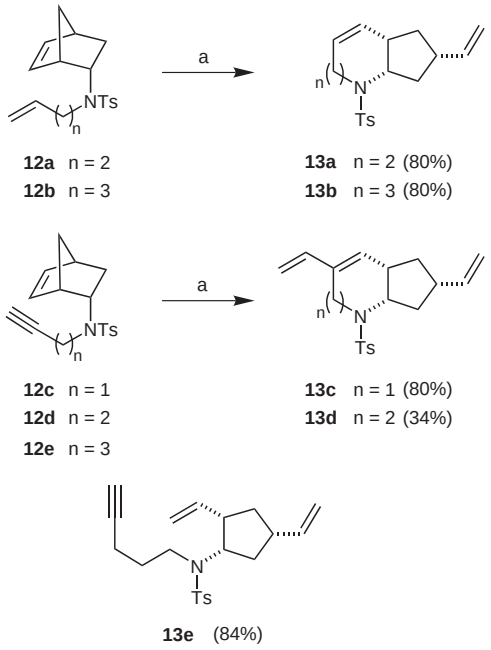


Scheme 3 *Reagents and conditions*: (a) allylamine, AcOH, THF, $NaBH(OAc)_3$; (b) $(Boc)_2O$, Et_3N, CH_2Cl_2 or BzCl, K_2CO_3, acetone–H_2O or TsCl, Et_3N, CH_2Cl_2; (c) Grubbs I (10 mol%), ethene, CH_2Cl_2.



Scheme 4 *Reagents and conditions*: (a) i) EtOCOCl, Et_3N, acetone, ii) NaN_3, H_2O, iii) 2 M HCl, Δ; (b) TsCl, Et_3N, CH_2Cl_2; (c) ROTs, K_2CO_3, MeCN, Δ.

In summary it is clear that the RRM reaction on suitably functionalised 2-aminonorbornene derivatives can be a powerful reaction for the synthesis of more complex fused bicycles. Substrates with unsaturation attached through an amide bond were found to be sensitive to the number of methylene units in the attached side chain, with success only when there was no possibility for chelation of the ruthenium. On all other substrates ring-rearrangement metathesis has proven to be efficient with the reaction



Scheme 5 *Reagents and conditions*: (a) Grubbs I (10 mol%), ethene, CH_2Cl_2.

only beginning to show reduced yields when the tether length increased. We are currently exploring the possibility of developing this methodology towards a synthesis of piperidine alkaloids such as the streptazolins.[20]

Acknowledgment

This work was supported by the EPSRC (AEN).

References and Notes

(1) (a) Bazan, G. C.; Oskam, J. H.; Cho, H. N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6889. (b) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378. (c) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141. (d) Schrock, R. R. *Acc. Chem. Res.* **1990**, *23*, 158.

(2) (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (b) Scwabb, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(3) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Dunne, A. M.; Mix, S.; Blechert, S. *Tetrahedron* **2003**, *59*, 2733.

(4) For reviews on the history, synthesis, and activity of the molybdenum-based metathesis catalysts, see: (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592. For recent reviews on ruthenium-based RCM, see: (b) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

(5) Blechert, S.; Connon, S. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.

(6) (a) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, 8179. (b) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334. (c) Winkler, J. D.; Asselin, S. M.; Shepard, S.; Yuan, J. *Org. Lett.* **2004**, *6*, 3821. (d) Wrobleski, A.; Sahasrabudhe, K.; Aube, J. *J. Am. Chem. Soc.* **2004**, *126*, 5475. (e) Chandler, C. L.; Phillips, A. J. *Org. Lett.* **2005**, *7*, 3493. (f) Yasui, H.; Yamamoto, S.; Saaki, D.; Kawasaki, S.; Watanabe, G.; Tadano, K.-I. *J. Org. Chem.* **2004**, *69*, 8789. (g) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817. (h) Quinn, K. J.; Isaacs, A. K.; Arvary, R. A. *Org. Lett.* **2004**, *6*, 4143. (i) Lesma, G.; Crippa, S.; Danieli, B.; Passarella, D.; Sacchetti, A.; Silvani, A.; Virdis, A. *Tetrahedron* **2004**, *60*, 6437. (j) Csaky, A. G.; Medel, R.; Murcia, M. C.; Plumet, J. *Helv. Chim. Acta* **2005**, *88*, 1387.

(7) *Handbook of Metathesis*, Vol. 2; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, **2003**, Chap. 2-4, 151–175.

(8) Arjona, O.; Csaky, A. G.; Murica, M. C.; Plumet, J. *Tetrahedron Lett.* **2000**, *41*, 9777.

(9) Ruckert, A.; Reisele, D.; Blechert, S. *Tetrahedron Lett.* **2001**, *42*, 5245.

(10) Hagiwara, H.; Katsumi, T.; Endou, S.; Hoshi, T.; Suzuki, T. *Tetrahedron* **2002**, *58*, 6651.

(11) (a) Voightmann, U.; Blechert, S. *Synthesis* **2000**, 893. (b) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, *3*, 1161. (c) Ovaa, H.; Stapper, C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H.; Blechert, S. *Tetrahedron* **2002**, *58*, 7503. (d) Arjona, O.; Csaky, A. G.; Medel, R.; Plumet, J. *J. Org. Chem.* **2002**, *67*, 1380. (e) Arjona, O.; Csaky, A. G.; Murcia, C.; Plumet, J. *ARKIVOC* **2002**, *(v)*, 171. (f) Arjona, O.; Csaky, A. G.; Leon, V.; Medel, R.; Plumet, J. *Tetrahedron Lett.* **2004**, *45*, 565. (g) Holub, N.; Neidhofer, J.; Blechert, S. *Org. Lett.* **2005**, *7*, 1227. (h) Groaz, E.; Banti, D.; North, M. *Tetrahedron Lett.* **2007**, *48*, 1927.

(12) (a) Maechling, S.; Norman, S. E.; Mckendrick, J. E.; Basra, S.; Knoppner, K.; Blechert, S. *Tetrahedron Lett.* **2006**, *47*, 189. (b) Nadany, A. E.; Mckendrick, J. E. *Synlett* **2006**, 2139. (c) Nadany, A. E.; Mckendrick, J. E. *Tetrahedron Lett.* **2007**, *48*, 4071.

(13) (a) Krieger, H. *Suom. Kemistil., B* **1963**, *36*, 68. (b) Freeman, P. K.; Balls, D. M.; Brown, D. J. *J. Org. Chem.* **1968**, *33*, 2211.

(14) (a) Longobardi, M.; Schenone, P.; Bargagna, A.; Berrino, L.; Matera, C.; Marmo, E. *Farmco Ed. Sci.* **1985**, *40*, 152. (b) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849. Analogous reduction of norborn-5-en-2-one: (c) Mayo, P.; Orlova, G.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5182. (d) Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* **1985**, *68*, 2100.

(15) **Spectroscopic Data for 5a**
^{1}H NMR (400 MHz, $CDCl_3$, 70 °C): δ = 1.35–1.38 (m, 1 H, CH_2CHN), 1.35–1.38 (m, 1 H, CH_2CHCHN), 2.12–2.33 (m, 1 H, CH_2CHN), 2.12–2.33 (m, 1 H, CH_2CHCHN), 2.12–2.33 (m, 1 H, $CHCH_2CHN$), 2.90–2.94 (m, 1 H, CHCHN), 3.69 (dt, 1 H, CHN, *J* = 10.5, 6.5 Hz), 4.06 (d, 1 H, CH_2Ph, *J* = 15.0 Hz), 4.90–5.03 (m, 2 H, $CH=CH_2$), 5.29 (d, 1 H, CH_2Ph, *J* = 15.0 Hz), 5.71 (ddd, 1 H, $CH=CH_2$, *J* = 17.0, 13.0, 7.0 Hz), 5.87 (dd, 1 H, HC=CH, *J* = 10.0, 2.5 Hz), 6.24 (dd, 1 H, HC=CH, *J* = 10.0, 3.0 Hz), 7.25–7.33 (m, 5 H, 5 × ArH). ^{13}C NMR (100 MHz, $CDCl_3$, 70 °C): δ = 36.6 (CHCHN), 38.6 (CH_2CHCHN), 39.0 (CH_2CHN), 40.1 ($CHCH_2CHN$), 48.5 (CH_2Ph), 58.7 (CHN), 114.5 ($CH=CH_2$), 122.0 (HC=CH), 127.8 (1 × ArH), 128.4 (2 × ArH), 129.0 (2 × ArH), 138.0 (1 × Ar), 141.2 ($CH=CH_2$), 143.4 (HC=CH), 162.7 (C=O). IR (thin film): 1610 (C=C), 1667 (C=O), 2955 (sat. C–H) cm^{-1}. MS: *m*/*z* calcd: 254.1546 [MH^+]; found: 254.1546.

(16) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.
(17) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388.
(18) **General Procedure for Olefin Metathesis, Synthesis of 8c**
A flask was charged with toluenesulfonyl amine **7c** (91 mg, 0.3 mmol) and CH_2Cl_2 (90 mL). Ethene gas was bubbled through the solution for 20 s. Then, Grubbs I catalyst (25 mg, 0.03 mmol) was added to the reaction. A balloon filled with ethene gas was placed over the flask and the reaction was allowed to stir at r.t. overnight. The reaction mixture was then concentrated and subjected to column chromatography eluting PE–Et_2O (19:1 to 4:1) to furnish **8c** as a colourless oil (89 mg), 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (ddd, 1 H, CH_2CHN, *J* = 13.5, 8.0, 4.0 Hz), 1.33 (dd, 1 H, $H_2CHCHC{=}CH$, *J* = 14.5, 7.5 Hz), 1.66 (dt, 1 H, $H_2CHCHC{=}CH$, *J* = 12.0, 6.5 Hz), 2.13 (td, 1 H, CH_2CHN, *J* = 16.0, 13.5 Hz), 2.41 (s, 3 H, CH_3), 2.41–2.43 (m, 1 H, $HCHC{=}CH$), 2.60–2.65 (br m, 1 H, $HCHC{=}CH_2$), 3.45–3.50 (m, 1 H, CH_2N), 4.06–4.10 (m, 1 H, CH_2N), 4.37 (dt, CHN, 1 H, *J* = 12.0, 7.0 Hz), 4.83–4.94 (m, 2 H, $HC{=}CH_2$), 5.51–5.61 (m, 2 H, HC=CH), 5.64 (ddd, 1 H, $HC{=}CH_2$, *J* = 17.5, 10.0, 7.5 Hz), 7.30 (app. d, 2 H, ArH, *J* = 8.5 Hz), 7.70 (app. d, 2 H, ArH, *J* = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (CH_3), 32.0 ($H_2CHCHC{=}CH$), 35.4 ($HCHC{=}CH_2$), 35.8 (CH_2CHN), 39.4 (CH_2N), 39.7 (HCHC=CH), 55.6 (CHN), 113.1 ($HC{=}CH_2$), 120.0 (HC=CH), 127.2 (2 × ArCH), 129.6 (2 × ArCH), 130.8 (HC=CH), 136.8 (1 × ArC), 142.4 ($HC{=}CH_2$), 143.2 (1 × Ar). IR (thin film): 1162, 1384 (SO_2), 2975 (sat. C–H) cm^{-1}. MS: *m*/*z* calcd for 303.1290 [M$^+$]; found: 303.1293.
(19) Parham, W. E.; Hunter, W. T.; Hanson, R. *J. Am. Chem. Soc.* **1951**, *73*, 5068.
(20) (a) Fangzheng, L.; Warshakoon, N. C.; Miller, M. J. *J. Org. Chem.* **2004**, *69*, 8836. (b) Kozikowski, A. P.; Park, P. *J. Am. Chem. Soc.* **1985**, *107*, 1736. (c) Kozikowski, A. P.; Park, P. *J. Org. Chem.* **1990**, *55*, 4668. (d) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115. (e) Yamada, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1996**, *118*, 1054. (f) Huang, S.; Comins, D. L. *Chem. Commun.* **2000**, 569.