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Preparation of Rearranged Allylic Isocyanates from the Reaction of Allylic Alcohols with 1-Cyano-4-dimethylaminopyridinium Bromide

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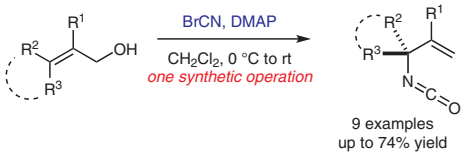

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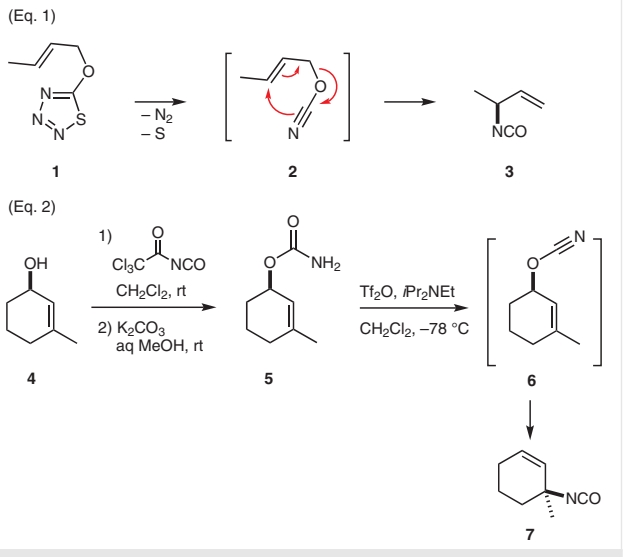
Abstract A shorter and less costly alternative to Ichikawa's [1,3]-transposition protocol for cyanates to isocyanates is described.

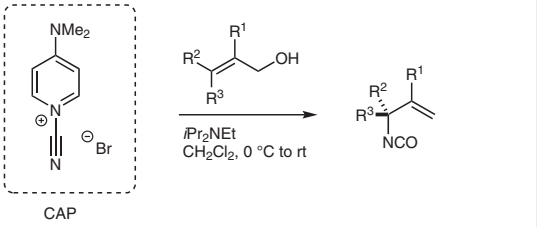
Key words sigmatropic rearrangement, [1,3]-transposition, allylic alcohol, methodology, total synthesis

[3,3]-Sigmatropic rearrangement of allylic cyanate to allylic isocyanate was first reported by Holms[1] in 1970 (Scheme 1, eq. 1). Chelotropic rupture of thiatriazole **1** provided allylic cyanate intermediate **2**, which immediately rearranged to allylic isocyanate **3**. Following this observation, several attempts have been made to make this reaction useful as a synthetic tool,[2] the most successful of which is the work by Ichikawa[3] in 1991. He reported an efficient method for the synthesis of allylic cyanate **6** by dehydration of allylic carbamate **5**, which, after [3,3]-sigmatropic rearrangement, provided the desired allylic isocyanate **7** (Scheme 1, eq. 2). Later in 1994, Ichikawa demonstrated that cyanate-to-isocyanate rearrangement is a truly concerted [3,3]-sigmatropic process involving highly selective [1,3]-chirality transfer to the newly-formed nitrogen-bearing center, as was postulated earlier by Holms.[3e]



Scheme 1 [3,3]-Sigmatropic rearrangement of allylic cyanates to allylic isocyanates

In this paper, we wish to report our observations on the reactions of allylic alcohols with in situ formed 1-cyano-4-dimethylaminopyridinium bromide (CAP): a convenient source of *electrophilic cyanide*,[4] Scheme 2.



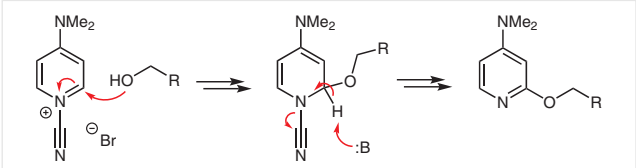
Scheme 2 Direct approach to rearranged allylic isocyanates by the reaction of allylic alcohols with CAP

4-(Dimethylamino)pyridine readily activates cyanogen bromide towards nucleophilic attack by forming CAP (Scheme 2). This reagent has been reported to produce cyanate derivatives of enzymes and various imidazole derivatives[4] but, surprisingly, this electrophilic activation of cyanogen bromide has not been exploited further in synthetic organic chemistry.[5] We felt that the conversion of cyanogen bromide into CAP should also serve as a convenient cyanat-

ing agent to prepare allylic cyanates from allylic alcohols directly, thus allowing rapid access to rearranged allylic isocyanates.

Treatment of 4-(dimethylamino)pyridine solution in dichloromethane with cyanogen bromide immediately provided a pale-yellow precipitate of CAP. Sequential addition of diisopropylethylamine and allylic alcohol furnished the rearranged allylic isocyanate in less than 30 minutes at 0 °C. The resulting isocyanates were characterized as stable ureas, produced by subsequent trapping with pyrrolidine. The generality of this approach was examined on a number of model substrates, as shown in Table 1.[6–11] The procedure works best for primary allylic alcohols. Propargyl alcohol **15a** (Table 1, entry 8) and sterically congested (*R*)-carvone derivative **16a** (entry 9) failed to react. We anticipate that the low yields for the transformation described herein can be attributed to electrophilicity of C-2 in CAP (DMAP numbering, Scheme 3). Unfortunately, no side product could be isolated from the reaction mixture. Finally, synthetic utility of this methodology in natural product synthesis was demonstrated on the preparation of Fukuyama's advanced intermediate **18** used in his total synthesis of tetrodotoxin (entries 10 and 11). Both geometric isomers of **17** were converted into Fukuyama's carbamate **18** in one synthetic operation as opposed to two operations previously reported.[11] Furthermore, none of the other diastereomeric product was observed during the course of this transformation, highlighting the stereoselectivity of the sigmatropic rearrangement approach to install the nitrogen functionality.

In summary, a shorter and less costly alternative to Ichikawa's [1,3]-transposition protocol for cyanates to isocyanates is described.



Scheme 3 Rationale for the low yields of [3,3]-sigmatropic rearrangement mediated by CAP and suggested possible side product

Table 1 Conversion of Allylic Alcohols into Rearranged Allylic Ureas[a]

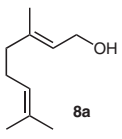
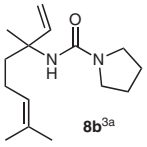
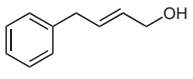
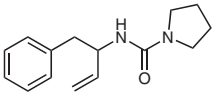
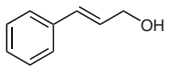
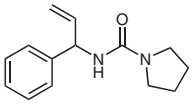
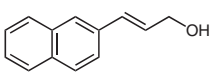
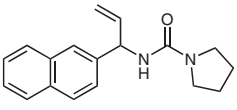
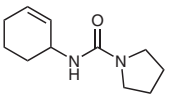
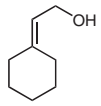
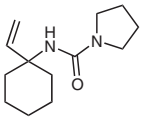
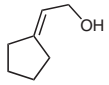
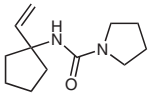
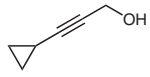
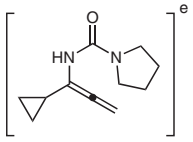
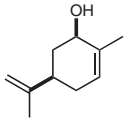
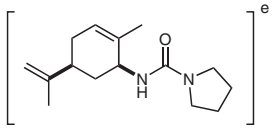
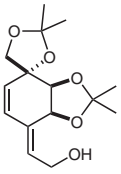
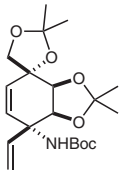
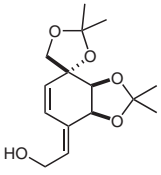
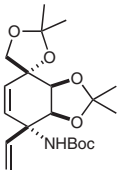
Entry	Substrate [Ref]	Product [Ref][b]	Yield (%)[c]
1	 **8a**	 **8b**[3a]	72
2	 **9a**[6]	 **9b**[3a]	46
3	 **10a**	 **10b**[3a]	52
4	 **11a**[7]	 **11b**	44
5	 **12a**	 **12b**[2,3a]	37

Table 1 (continued)

Entry	Substrate [Ref]	Product [Ref][b]	Yield (%)[c]
6	 **13a**[8]	 **13b**	74
7	 **14a**[8]	 **14b**	35
8	 **15a**[9]	 **15b**	–
9	 **16a**[10]	 **16b**	–
10[d]	 **17a**[11a]	 **18**[11]	39
11[d]	 **17b**[11b]	 **18**[11]	35

[a] Reactions were performed according to the typical procedure reported for **8b**.
[b] Isocyanates were characterized as stable ureas, which were produced by reaction with pyrrolidine.
[c] Isolated yields after chromatographic purification.
[d] Intermediate isocyanate was trapped with LiO*t*-Bu (1.0 M in THF).
[e] Not formed.

^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz Bruker spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) with reference to non-deuterated residual $CHCl_3$ solvent peak at 7.26 ppm. Data for proton spectra are reported as of following format: chemical shift (multiplicity, standard abbreviations), coupling constants (Hz), integration. Chemical shifts for ^{13}C NMR were reported in ppm relative to the central line of a triplet at 77.16 ppm for $CDCl_3$. Optical rotations were measured on a Mandel Rudolph Research Analytical Automatic Polarimeter at 589 nm with a cell length of 50 mm. IR spectra were recorded on a Bruker ATR Fourier Transform Infrared Spectrophotometer and were reported in wavenumbers (cm^{-1}). Mass spectra and high-resolution mass spectra were obtained by the analytical division at Brock University. Melting points were determined on a Hoover Unimelt apparatus and are uncorrect-

ed. Analytical TLC was performed on EMD Silica Gel 60 Å 250 µm plates with F-254 indicator, while column chromatography was performed using Silicycle SiliaFlash P60 (230–400 mesh).

CH_2Cl_2 was freshly distilled from CaH_2 prior to use. Commercial *n*-hexane was re-distilled prior to column chromatography to minimize the grease content. *i*-Pr_2NEt (Hünig's base) was distilled from KOH and stored over KOH pellets. All other chemicals/solvents were purchased from either Sigma-Aldrich or Oakwood Chemicals and used as received. All reactions were conducted under an argon atmosphere using standard Schlenk techniques.

N-(3,7-Dimethylocta-1,6-dien-3-yl)pyrrolidine-1-carboxamide (8b);[3a]

Typical Procedure

To a stirred solution of DMAP (275 mg, 2.25 mmol) in CH_2Cl_2 (4 mL) was added BrCN (3.0 M in CH_2Cl_2, 0.75 mL, 2.25 mmol) dropwise at 0 °C. A pale-yellow precipitate of 1-cyano-4-dimethylaminopyridinium bromide was immediately formed and the mixture was allowed to stir for another 5 min whereupon *i*-Pr_2NEt (0.2 mL, 1.13 mmol) followed by geraniol (**8a**; 121 mg, 0.75 mmol) in CH_2Cl_2 (0.5 mL) were added at at 0 °C. The resulting reaction mixture was warmed up to r.t. and stirred until the full consumption of the starting material (*ca.* 20 min). The mixture was cooled to 0 °C and pyrrolidine (0.43 mL, 5.25 mmol) was slowly added. Cooling bath was removed and the mixture was stirred for another 1 h at r.t. Then, volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/*n*-hexane 1:1) to furnish urea **8b** as a colorless oil; yield: 187 mg (72%).

IR (neat): 3340, 2967, 2927, 2869, 1637, 1523, 1450, 1374, 1195, 911, 765 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.97 (dd, *J* = 17.3, 11.0 Hz, 1 H), 5.20–4.96 (m, 3 H), 4.21 (s, 1 H), 3.36–3.19 (m, 4 H), 2.00–1.90 (m, 2 H), 1.90–1.83 (m, 4 H), 1.79–1.67 (m, 2 H), 1.65 (s, 3 H), 1.57 (s, 3 H), 1.44 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 144.8, 131.7, 124.5, 111.7, 56.7, 45.5, 40.3, 25.7, 25.2, 22.9, 17.8.

HRMS (EI+): *m*/*z* calcd for $C_{15}H_{26}N_2O$: 250.2045; found: 250.2040.

N-(1-Phenylbut-3-en-2-yl)pyrrolidine-1-carboxamide (9b)[3a]

Yield: 85 mg (46%), starting from **9a** (111 mg, 0.75 mmol); white solid; mp 76–78 °C (EtOAc).

IR (neat): 3280, 2927, 2869, 1619, 1521, 1391, 913, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.13 (m, 5 H), 5.87 (ddd, *J* = 17.1, 10.4, 5.4 Hz, 1 H), 5.12 (dt, *J* = 17.1, 1.4 Hz, 1 H), 5.08 (dt, *J* = 5.4, 1.4 Hz, 1 H), 4.77–4.64 (m, 1 H), 4.11 (d, *J* = 8.0 Hz, 1 H), 3.37–3.22 (m, 4 H), 2.99–2.81 (m, 2 H), 1.97–1.82 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 139.0, 137.8, 129.8, 128.4, 126.6, 114.6, 53.0, 45.5, 25.6.

HRMS (EI+): *m*/*z* calcd for $C_{15}H_{20}N_2O$: 244.1576; found: 244.1572.

N-(1-Phenylallyl)pyrrolidine-1-carboxamide (10b)[3a]

Yield: 90 mg (52%), starting from **10a** (100 mg, 0.75 mmol); colorless oil.

IR (neat): 3321, 2969, 2869, 1612, 1517, 1390, 1198, 992, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 5 H), 6.05 (ddd, *J* = 17.3, 10.1, 5.4 Hz, 1 H), 5.64–5.50 (m, 1 H), 5.26–5.21 (m, 1 H), 5.21–5.17 (m, 1 H), 4.51 (d, *J* = 7.8 Hz, 1 H), 3.41–3.26 (m, 4 H), 1.94–1.82 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 142.0, 138.8, 128.7, 127.4, 127.3, 115.3, 56.1, 45.6, 25.6.

HRMS (EI+): *m*/*z* calcd for $C_{14}H_{18}N_2O$: 230.1419; found: 230.1413.

N-[1-(Naphthalen-2-yl)allyl]pyrrolidine-1-carboxamide (11b)

Yield: 93 mg (44%), starting from **11a** (138 mg, 0.75 mmol); white solid; mp 131–132 (EtOAc/*n*-hexane).

IR (neat): 3319, 2970, 2870, 1612, 1517, 1378, 1206 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.74 (m, 4 H), 7.52–7.40 (m, 3 H), 6.16 (ddd, *J* = 17.4, 10.0, 5.3 Hz, 1 H), 5.84–5.66 (m, 1 H), 5.35–5.17 (m, 2 H), 4.54 (d, *J* = 8.0 Hz, 1 H), 3.51–3.24 (m, 4 H), 1.99–1.82 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 139.4, 138.7, 133.4, 132.8, 128.4, 128.0, 127.6, 126.2, 125.9, 125.8, 125.7, 115.6, 56.1, 45.6, 25.6.

HRMS (EI+): *m*/*z* calcd for $C_{18}H_{20}N_2O$: 280.1576; found: 280.1572.

N-(Cyclohex-2-en-1-yl)pyrrolidine-1-carboxamide (12b)[2,3a]

Yield: 54 mg (37%), starting from **12a** (74 mg, 0.75 mmol); white solid; mp 88–91 °C (EtOAc/*n*-hexane).

IR (neat): 3297, 2930, 2849, 1612, 1514, 1294, 1192, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.86–5.74 (m, 1 H), 5.70–5.56 (m, 1 H), 4.45–4.30 (m, 1 H), 4.20–4.03 (m, 1 H), 3.31 (m, 4 H), 2.04–1.93 (m, 2 H), 1.93–1.82 (m, 5 H), 1.69–1.58 (m, 2 H), 1.58–1.45 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 130.3, 129.3, 45.6, 45.5, 30.5, 25.7, 25.1, 19.9.

HRMS (EI+): *m*/*z* calcd for $C_{11}H_{18}N_2O$: 194.1419; found: 194.1417.

Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34. Found: C, 67.98; H; 9.19.

N-(1-Vinylcyclohexyl)pyrrolidine-1-carboxamide (13b)

Yield: 123 mg (74%), starting from **13a** (95 mg, 0.75 mmol); white solid; mp 101–102 °C (EtOAc/*n*-hexane).

IR (neat): 3313, 2971, 2851, 1618, 1524, 1377, 910 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.07 (dd, *J* = 17.5, 10.7 Hz, 1 H), 5.10 (dd, *J* = 17.5, 1.1 Hz, 1 H), 5.04 (dd, *J* = 10.7, 1.1 Hz, 1 H), 4.05 (s, 1 H), 3.40–3.25 (m, 4 H), 2.15–2.00 (m, 2 H), 1.96–1.84 (m, 4 H), 1.68–1.18 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 145.2, 111.7, 55.8, 45.6, 35.7, 25.8, 25.7, 22.1.

HRMS (EI+): *m*/*z* calcd for $C_{13}H_{22}N_2O$: 222.1732; found: 222.1730.

Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97. Found: C, 70.24; H, 10.17.

N-(1-Vinylcyclopentyl)pyrrolidine-1-carboxamide (14b)

Yield: 55 mg (35%), starting from **14a** (84 mg, 0.75 mmol); colorless oil.

IR (neat): 3336, 2949, 2867, 1626, 1520, 1373, 903 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.07 (dd, *J* = 17.4, 10.6 Hz, 1 H), 5.06 (dd, *J* = 17.4, 1.0 Hz, 1 H), 5.00 (dd, *J* = 10.6, 1.0 Hz, 1 H), 4.19 (s, 1 H), 3.39–3.15 (m, 4 H), 2.06–1.59 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 143.5, 111.3, 64.6, 45.6, 38.6, 25.7, 23.3.

HRMS (EI+): *m*/*z* calcd for $C_{12}H_{20}N_2O$: 208.1576; found: 208.1571.

Anal. Calcd for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68. Found: C, 69.27; H, 9.94.

***tert*-Butyl {(3a*S*,4*R*,7*R*,7a*S*)-2,2,2′,2′-Tetramethyl-7-vinyl-7,7a-dihydro-3a*H*-spiro[benzo[*d*][1,3]dioxole-4,4′-[1,3]dioxolan]-7-yl}carbamate (18)**[11]

Yield: 6 mg (39%), starting from **17a** (11 mg, 0.04 mmol); yield: 11 mg (35%), starting from **17b** (23 mg, 0.08 mmol); yellow oil; $[\alpha]_D^{22}$+9.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.10 (d, *J* = 9.9 Hz, 1 H), 6.04 (dd, *J* = 16.9, 10.6 Hz, 1 H), 5.90 (d, *J* = 9.9 Hz, 1 H), 5.26 (d, *J* = 10.6 Hz, 1 H), 5.22 (d, *J* = 16.9 Hz, 1 H), 5.08 (s, 1 H), 4.64 (d, *J* = 7.5 Hz, 1 H), 4.44 (d, *J* = 7.5 Hz, 1 H), 4.25 (d, *J* = 8.8 Hz, 1 H), 3.72 (d, *J* = 8.8 Hz, 1 H), 1.43 (s, 3 H), 1.42 (s, 9 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.33 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.7, 138.7, 134.8, 132.2, 115.6, 110.1, 109.0, 79.9, 79.7, 78.7, 78.0, 71.5, 57.4, 28.6, 27.1, 26.7, 26.3, 24.6.

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Supporting Information

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References

(1) (a) Christophersen, C.; Holms, A. *Acta Chem. Scand.* **1970**, *24*, 1512. For the related [3,3]-sigmatropic rearrangement of allylic thiocyanates see: (b) Smith, P. A.; Emerson, D. W. *J. Am. Chem. Soc.* **1960**, *82*, 3076. For other examples of [3,3]-sigmatropic rearrangements see: (c) Ramadhar, T. R.; Kawakami, J.; Batey, R. A. *Synlett* **2017**, *28*, 2865. (d) Ramb, D. C.; Kost, L.; Haufe, G. *Chimia* **2014**, *68*, 436. (e) Mingat, G.; MacLellan, P.; Laars, M.; Clayden, J. *Org. Lett.* **2014**, *16*, 1252.

(2) Overman, L. E.; Kakimoto, M. *J. Org. Chem.* **1978**, *43*, 4563.

(3) For the discovery of this reaction, see: (a) Ichikawa, Y. *Synlett* **1991**, 238. For recent reviews in this field, see: (b) Ichikawa, Y. *Synlett* **2007**, 2927. (c) Mailyan, A. K.; Eickhoff, J. A.; Minakova, A. S.; Gu, Z.; Lu, P.; Zakarian, A. *Chem. Rev.* **2016**, *116*, 4441. For the detailed experimental procedure, see: (d) Ichikawa, Y.; Kariya, N.; Hasegawa, T. *Org. Synth.* **2013**, *90*, 271. For the stereochemistry of the reaction, see: (e) Ichikawa, Y.; Tsoboi, K.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2791.

(4) (a) Whitten, J. P.; Mcarthy, J. R.; Matthews, D. P. *Synthesis* **1988**, 470. (b) Waselman, M.; Guibe-Jampel, E.; Raoult, A.; Busse, W. D. *J. Chem. Soc., Chem. Commun.* **1976**, 21.

(5) Enehydroxylamines react with CAP to afford imidazolidinones in a similar 3,3-sigmatropic rearrangement reaction: Reis, L. V.; Lobo, A. M.; Prabhakar, S.; Duarte, M. P. *Eur. J. Org. Chem.* **2003**, 190.

(6) Wilson, R.; Bedard, K.; Baidilov, D.; Tius, M.; Hudlicky, T. *Tetrahedron Lett.* **2018**, *59*, 2467.

(7) Okamoto, R.; Tanaka, K. *Org. Lett.* **2013**, *15*, 2112.

(8) Szcześniak, P.; Pieczykolan, M.; Stecko, S. *J. Org. Chem.* **2016**, *81*, 1057.

(9) Mainetti, E.; Fresterbank, L.; Malacria, M. *Synlett* **2002**, 923.

(10) Valeev, R. F.; Khasanova, L. S.; Miftakhov, M. S. *Russ. J. Org. Chem.* **2010**, *46*, 670.

(11) (a) Maehara, T.; Motoyama, K.; Toma, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2017**, *56*, 1549; Angew. Chem. 2017, 129, 1571. (b) Baidilov, D.; Rycek, L.; Trant, J. F.; Froese, J.; Murphy, B.; Hudlicky, T. *Angew. Chem. Int. Ed.* **2018**, *57*, 10994; *Angew. Chem.* **2018**, *130*, 11160.