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An Efficient Synthesis of *de novo* Imidates via *Aza*-Claisen Rearrangements of *N*-Allyl Ynamides

Kyle A. DeKorver, **Troy D. North**, and **Richard P. Hsung***
Division of Pharmaceutical Sciences and Department of Chemistry, 777 Highland Avenue, Rennebohm Hall, University of Wisconsin, Madison, WI 53705

Abstract

A novel thermal 3-*aza*-Claisen rearrangement of *N*-allyl ynamides for the synthesis of α-allyl imidates is described. Also, a sequential *aza*-Claisen, Pd-catalyzed Overman rearrangement is described for the synthesis of azapine-2-ones.

Keywords

Ynamide; *aza*-Claisen; Imidate; Ketenimine; Overman rearrangement

We recently reported the *de novo* synthesis of pharmacologically useful amidines from *N-allyl* ynamides[1,2] featuring either a Pd-catalyzed[3] *N*-to-*C* allyl transfer *or* unprecedented thermal[3,4] 3-*aza*-*Claisen*[5] rearrangement followed by trapping of the *in situ* generated ketenimine6 with amine nucleophiles. There has been great interest within the synthetic community on preparing amidines and imidates,[7] most commonly through interception of the ketenimine intermediate produced during a Cu-catalyzed Huisgen-[3+2] cycloaddition of azides and alkynes.[8-]10 Herein, we describe our efforts at the synthesis of imidates via trapping of ketenimines **3** formed via *aza*-Claisen rearrangement of ynamides **1** in the presence of alcoholic nucleophiles.

It was quickly discovered that the nucleophilicity of even simple alcohols such as methanol and ethanol was not sufficient to yield imidates **6** despite the alcohols being used in 200 fold excess [Scheme 2]! Furthermore, attempts to trap ketenimine **7** generated from ynamide **5a** with more nucleophilic sodium methoxide led to cleavage of the *N*-toluenesulfonamide protecting group furnishing nitrile **8** in quantitative yield.

Our subsequent attempts to carry out this transformation intramolecular were also met with difficulty. Alcohol **10** could be prepared by simple TBAF mediated desilylation of **9**. Upon heating of **10** in toluene, the only isolable products were nitrile **11** formed through a 1,3-sulfonyl[4,11] transfer during the ketenimine intermediate and *p*-toluenesulfonamide, which implies that the *aza*-Claisen did in fact occur but was not productive towards imidate formation. Alternatively, when **10** was treated with sodium hydride to increase the nucleophilicity of the oxygen and then heated to 80 °C, only enamides **13** and **14** were formed through 5-*exo*-dig and 6-*endo*-dig cyclization onto the ynamide, respectively. Since this was too nucleophilic for the *aza*-Claisen to occur, we instead opted to cleave the silyl protecting group of ynamide **9** *in situ* to trigger the cyclization, however again only nitrile **12** was found, demonstrating that the 1,3-sulfonyl shift is quite facile.

Fax: 608-262-5345. rhsung@wisc.edu.

Finally, we found that heating of ynamides **1** in alcoholic solvents in the presence of 4Å molecular sieves led to imidates **4** in moderate to excellent yields. The reaction conditions tolerated both silyl and aryl-terminated ynamides and showed moderate sensitivity to the electron-withdrawing nature of *N*-sulfonyl protecting group with *p*-Ns providing the corresponding imidates in the highest yields due to increased electrophilicity of the ketenimine [entries 3 vs. 6 and 4 vs. 7]. Notably, there was no reaction observed with *N*-Boc or *N*-Ac ynamides even at temperatures of >140 °C, indicating the strong electronic effect on the initial *aza*-Claisen rearrangement. There was also a clear sensitivity to sterics with the use of more sterically hindered nucleophiles giving rise to nitriles through the competing intramolecular 1,3-sulfonyl shift in the ketenimine intermediate when R = Ph [entries 8 vs. 10]. Interestingly, no nitrile formation was observed in the cases where R = TIPS, likely due to the increased steric bulk preventing the necessary migration.

Next, we sought to develop a tandem *aza*-Claisen–Overman[12] rearrangement, which followed by RCM may be used for the synthesis of useful azapine-2-one scaffolds **17**. Ynamide **5a** underwent reaction with allyl alcohol to yield diallyl imidate **15** in moderate yield. Unfortunately, our attempts at a thermal Overman rearrangement were unsuccessful, as heating of **15** in *n*-decane at 140 °C even for several days resulted in no formation of **16**. However, to our delight, exposure of **15** to a catalytic amount of $PdCl_2(PhCN)_2$ at room temperature led to [3,3] rearrangement product **16** in >95% yield.[9b] With **16** in hand, efficient ring-closing metathesis[13] was achieved using Grubbs' first generation catalyst to provide azapine-2-one **17** in 90% yield.

Herein, we have disclosed a novel synthesis of α-allyl imidates via a thermal 3-*aza*-Claisen rearrangement of *N*-allyl ynamides. We found that it is necessary to use the alcohol as solvent to avoid a competing 1,3-sulfonyl transfer forming nitriles. Also, the use of alkoxides intermolecularly led to efficient desulfonylation, while intramolecularly gave 5-*exo*-dig cyclization of the alkoxide onto the ynamide. In addition, we have demonstrated the use of a sequential 3-*aza*-Claisen–Overman rearrangement, which followed by ring-closing metathesis may be used to provide access to azapine-2-one scaffolds.

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Appendix

Selected Experimental Procedures and Characterizations

Synthesis of Nitrile 8

To a stirring solution of ynamide **5a** (75.0 mg, 0.19 mmol) in toluene (2 mL) at rt was slowly added freshly prepared NaOMe (31.0 mg, 0.58 mmol). After addition, the reaction mixture was sealed under dry nitrogen and heated to 100 °C for 1 h. Over the course of the reaction, TsOMe was observed to precipitate out of solution and was subsequently removed by filtration of the crude reaction mixture through a plug of Celite™ to afford the pure nitrile **8** (45.6 mg, 0.19 mmol, >95% yield) as a colorless oil.

R_f = 0.45 [4:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 – 1.41 (m, 21H), 2.05 (dd, 1H, *J* = 7.5, 4.0 Hz), 2.28 – 2.34 (m, 1H), 2.35 – 2.44 (m, 1H), 5.14 (d, 1H, *J* = 10.5 Hz), 5.17 (d, 1H, *J* = 18.0 Hz), 5.88 – 5.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 14.4, 18.9, 31.8, 117.2, 122.7, 136.2; IR (film) cm^{-1} 2946m, 2869m, 2222w, 1595m, 1377m; mass spectrum (APCI): m/e (% relative intensity) 238 (100) $(M+H)^+$.

Synthesis of Alcohol 10

To a stirring solution of ynamide **9** (315.0 mg, 0.77 mmol) in THF (2 mL) at rt was slowly added TBAF (0.85 mL, 1.0 *M* in THF). After 2 h, the solvent was removed via rotary evaporation and the crude oil was purified by flash silica gel column chromatography [isocratic eluent: 1:1 hexanes/EtOAc] to afford the alcohol **10** (191.0 mg, 0.65 mmol, 85% yield) as a pale yellow oil.

R_f = 0.09 [2:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (brs, 1H), 1.73 (pent, 2H, *J* = 6.5 Hz), 2.38 (t, 2H, *J* = 7.0 Hz), 3.71 (d, 2H, *J* = 7.0 Hz), 3.91 (d, 2H, *J* = 7.0 Hz), 5.19 (d, 1H, *J* = 10.5 Hz), 5.24 (d, 1H, *J* = 17.5 Hz), 5.72 (ddt, 1H, *J* = 17.5, 10.5, 7.0 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 7.78 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.4, 21.9, 31.8, 54.4, 61.9, 69.9, 73.8, 120.0, 128.0, 130.0, 131.4, 135.0, 144.8; IR (film) cm^{-1} 3200brs, 2981m, 2878m, 1644m; mass spectrum (APCI): m/e (% relative intensity) 294 (100) $(M+H)^+$.

Nitrile 12. R_f = 0.41 [8:1 hexanes/EtOAc]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.86 (s, 9H), 1.66 – 1.85 (m, 2H), 2.05 (dd, 2H, *J* = 8.4, 6.8 Hz), 2.48 (s, 3H), 2.67 – 2.79 (m, 2H), 3.59 (t, 2H, *J* = 6.0 Hz), 5.24 (d, 1H, *J* =16.8 Hz), 5.26 (d, 1H, *J* = 10.0 Hz), 5.82 (ddt, 1H, *J* = 17.6, 10.0 Hz, 7.2 Hz), 7.40 (d, 2H, *J* = 8.0 Hz), 7.88 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.2, 18.4, 22.0, 26.1, 28.3, 28.7, 36.8, 62.1, 65.8, 116.9, 121.9, 129.8, 130.2, 131.0, 131.7; IR (film) cm^{-1} 2929m, 2857m, 2238w, 1596m, 1331s, 1150s; mass spectrum (APCI): m/e (% relative intensity) 408 (100) $(M+H)^+$; HRMS (ESI): m/e calcd for $C_{21}H_{33}NO_3SSiNa$ 430.1843, found 430.1860.

Synthesis of 13

To a solution of ynamide **10** (75.0 mg, 0.26 mmol) in THF (5 mL) at 0 °C was added NaH (19.0 mg, 0.46 mmol, 60% wt/wt in mineral oil). The reaction mixture was warmed to rt and stirred for 20 min to allow for complete deprotonation and then sealed under dry nitrogen and heated to 85 °C for 3 h. The reaction mixture was quenched with water and the organic phase was extracted with EtOAc, and then dried over Na_2SO_4. Removal of the solvent by rotary evaporation and purification by flash silica gel column chromatography [isocratic eluent: 4:1 hexanes/EtOAc] afforded **13** (50.0 mg, 0.17 mmol, 65% yield) as a colorless oil.

13: R_f = 0.35 [4:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90 (pent, 2H, *J* = 9.5 Hz), 2.40 (s, 3H), 2.49 (td, 2H, *J* = 9.5, 2.0 Hz), 3.96 (t, 2H, *J* = 8.0 Hz), 3.97 (d, 2H, *J* = 8.5 Hz), 4.86 (s, 1H), 5.06 (dd, 1H, *J* = 13.0, 2.0 Hz), 5.14 (dd, 1H, *J* = 20.0, 2.0 Hz), 5.76 (ddt, 1H, *J* = 20.0, 13.0, 8.5 Hz), 7.26 (d, 2H, *J* = 9.5 Hz), 7.70 (d, 2H, *J* = 9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 24.6, 28.4, 52.3, 72.0, 94.9, 117.6, 127.7, 129.4, 134.1, 136.9, 143.1, 157.4; IR (film) cm^{-1} 3055m, 2980m, 1597s, 1337s; mass spectrum (APCI): m/e (% relative intensity) 294 (100) $(M+H)^+$; HRMS (ESI): m/e calcd for $C_{15}H_{19}NO_3SNa$ 316.0978, found 316.0986.

14: R_f = 0.38 [4:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (pent, 2H, *J* = 7.0 Hz), 2.43 (s, 3H), 2.80 (td, 2H, *J* = 8.0, 2.0 Hz), 3.66 (d, 2H, *J* = 6.5 Hz), 4.16 (t, 2H, *J* = 6.5 Hz), 4.76 (t, 1H, *J* = 2.0 Hz), 5.08 – 5.13 (m, 2H), 5.70 (ddt, 1H, *J* = 17.0, 10.0, 6.5 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 7.67 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 24.4, 28.1, 54.8, 72.1, 97.8, 119.1, 127.9, 129.8, 133.1, 135.0, 143.5, 166.8; mass spectrum (APCI): m/e (% relative intensity) 294 (20) $(M+H)^+$.

General Procedure for the Synthesis of Imidates 4a-4l

To a flame-dried vial containing 4Å MS was added the appropriate ynamide and dry alcohol solvent (0.04 *M* in ynamide). The reaction mixture was sealed under dry nitrogen and heated

to 75 – 95 °C for 2 – 5 d. Upon cooling to rt, the mixture was filtered through a plug of Celite™. Removal of the alcohol solvent *in vacuo* followed by flash silica gel column chromatography afforded the respective imidate.

Imidate 4a—R_f = 0.45 [4:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, 9H, *J* = 7.5 Hz), 1.20 (d, 9H, *J* = 7.5 Hz), 1.35 (sept, 3H, *J* = 7.5 Hz), 2.46 (s, 3H), 2.50 (m, 1H), 2.62 (ddd, 1H, *J* = 20.5, 12.5, 8.5 Hz), 3.71 (dd, 1H, *J* = 3.0, 12.0 Hz), 3.73 (s, 3H), 4.92 (dd, 1H, *J* = 10.0, 1.0 Hz), 5.00 (ddt, 1H, *J* = 17.0, 3.0, 1.5 Hz), 5.73 (dddd, 1H, *J* = 22.5, 14.0, 8.5, 5.5 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.86 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 19.1, 19.1, 21.8, 32.6, 34.2, 54.0, 115.8, 126.9, 129.4, 137.5, 140.2, 143.0, 178.4; IR (film) cm^{-1} 2948m, 2868m, 1582s, 1288s; mass spectrum (APCI): m/e (% relative intensity) 424 (100) $(M+H)^+$; HRMS (ESI): m/e calcd for $C_{22}H_{37}NO_3SSiNa$ 446.2156, found 446.2161.

Imidate 4b—R_f = 0.38 [4:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (d, 9H, *J* = 7.5 Hz), 1.16 (d, 9H, *J* = 7.5 Hz), 1.24 (t, 3H, *J* = 7.0 Hz), 1.31 (sept, 3H, *J* = 7.5 Hz), 2.41 (s, 3H), 2.59 (dt, 1H, *J* = 13.5, 9.0 Hz), 3.64 (dd, 1H, *J* = 12.5, 3.0 Hz), 4.04 – 4.17 (m, 2H), 4.87 (d, 1H, *J* = 10.0 Hz), 4.95 (d, 1H, *J* = 16.5 Hz), 5.63 – 5.73 (m, 1H), 7.26 (d, 2H, *J* = 7.5 Hz), 7.80 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 13.9, 19.1, 19.1, 21.7, 32.4, 34.2, 64.2, 115.7, 126.8, 129.3, 137.5, 140.2, 142.8, 177.8; IR (film) cm^{-1} 2948m, 2871m, 1965w, 1575s, 1289s, 1155s; mass spectrum (APCI): m/e (% relative intensity) 438 (100) $(M+H)^+$; HRMS (ESI): m/e calcd for $C_{23}H_{39}NO_3SSiNa$ 460.2313, found 460.2295.

Imidate 4c—R_f = 0.19 [15:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, 9H, *J* = 7.5 Hz), 1.14 (d, 3H, *J* = 6.0 Hz), 1.15 (d, 9H, *J* = 7.5 Hz), 1.25 (d, 3H, *J* = 6.0 Hz), 1.31 (sept, 3H, *J* = 7.5 Hz), 2.41 (s, 3H), 2.40 – 2.48 (m, 1H), 2.57 (dt, 1H, *J* = 14.0, 8.5 Hz), 2.84 (dd, 1H, *J* = 12.0, 3.0 Hz), 4.86 (d, 1H, *J* = 10.0 Hz), 4.96 (dd, 1H, *J* = 17.0, 1.0 Hz), 5.03 (sept, 1H, *J* = 6.0 Hz), 5.68 (dddd, 1H, *J* = 17.0, 10.0, 8.5, 5.5 Hz), 7.26 (d, 2H, *J* = 8.0 Hz), 7.80 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 19.2, 21.6, 21.7, 21.8, 32.4, 34.4, 71.9, 115.8, 126.8, 129.3, 137.4, 140.4, 142.7, 177.2; IR (film) cm^{-1} 2946m, 2868m, 1570s, 1464m, 1287m, 1153s; mass spectrum (APCI): m/e (% relative intensity) 410 (100) $(M–propene+H)^+$; HRMS (ESI): m/e calcd for $C_{24}H_{41}NO_3SSiNa$ 474.2469, found 474.2446.

Imidate 4d—R_f = 0.41 [4:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (d, 9H, *J* = 9.5 Hz), 1.15 (d, 9H, *J* = 9.5 Hz), 1.31 (sept, 3H, *J* = 9.5 Hz), 1.50 – 1.82 (m, 8H), 2.41 (s, 3H), 2.40 – 2.47 (m, 1H), 2.55 (dt, 1H, *J* =18.0, 10.5 Hz), 3.64 (dd, 1H, *J* = 15.5, 4.0 Hz), 4.86 (d, 1H, *J* = 12.5 Hz), 4.94 (d, 1H, *J* = 21.0 Hz), 5.12 – 5.16 (m, 1H), 5.62 – 5.74 (m, 1H), 7.25 (d, 2H, *J* = 10.0 Hz), 7.80 (d, 2H, *J* = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 19.2, 21.7, 23.8, 24.2, 32.2, 32.9, 34.4, 81.4, 115.6, 126.8, 129.3, 137.6, 140.5, 142.7, 117.5; IR (film) cm^{-1} 2946m, 2869m, 1571s, 1463w, 1287m, 1153s; mass spectrum (APCI): m/e (% relative intensity) 410 (100) $(M\text{-cyclopentene}+H)^+$; HRMS (ESI): m/e calcd for $C_{26}H_{43}NO_3SSiNa$ 500.2626, found 500.2618.

Imidate 4e—R_f = 0.42 [4:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (d, 9H, *J* = 9.0 Hz), 1.16 (d, 9H, *J* = 9.5 Hz), 1.26 (t, 3H, *J* = 9.0 Hz), 1.32 (sept, 3H, *J* = 9.5 Hz), 2.44 – 2.52 (m, 1H), 2.61 (dt, 1H, *J* = 17.5, 11.0 Hz), 3.59 (dd, 1H, *J* = 15.5, 4.0 Hz), 4.05 – 4.15 (m, 2H), 4.93 (d, 1H, *J* = 12.5 Hz), 4.99 (d, 1H, *J* = 21.0 Hz), 5.71 – 5.82 (m, 1H), 8.09 (d, 2H, *J* = 11.5 Hz), 8.32 (d, 2H, *J* = 11.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 13.9, 19.0, 19.1, 33.5, 34.3, 64.8, 116.1, 124.2, 128.0, 137.3, 148.6, 179.5; IR (film) cm^{-1} 2943w,

2868w, 1566s, 1531s, 1295s, 1159s; mass spectrum (APCI): m/e (% relative intensity) 469 (100) $(M+H)^+$; HRMS (ESI): m/e calcd for $C_{22}H_{36}N_2O_5SSiNa$ 491.2007, found 491.2007.

Imidate 4f—R_f = 0.27 [15:1 hexanes/EtOAc]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, 9H, *J* = 7.2 Hz), 1.15 (d, 3H, *J* = 6.4 Hz), 1.17 (d, 9H, *J* = 7.6 Hz), 1.28 (d, 3H, *J* = 6.4 Hz), 1.32 (sept, 3H, *J* = 7.6 Hz), 2.46 – 2.52 (m, 1H), 2.60 (dt, 1H, *J* = 14.4, 8.8 Hz), 3.61 (dd, 1H, *J* = 12.0, 3.6 Hz), 4.93 (d, 1H, *J* = 10.0 Hz), 4.96 – 5.04 (m, 2H), 5.76 (dddd, 1H, *J* = 17.0, 10.0, 8.8, 5.2 Hz), 8.10 (d, 2H, *J* = 9.2 Hz), 8.33 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 19.1, 19.1, 21.5, 21.8, 33.4, 34.4, 72.9, 116.1, 124.2, 128.0, 137.3, 148.7, 149.9, 178.9; IR (film) cm^{-1} 2946m, 2869m, 1562s, 1531s, 1349s, 1296s, 1156s; mass spectrum (APCI): m/e (% relative intensity) 441 (30) $[M\text{-propene}+H]^+$; HRMS (ESI): m/e calcd for $C_{23}H_{38}N_2O_5SSiNa$ 505.2163, found 505.2164.

Imidate 4g—R_f = 0.36 [10:1 hexanes/EtOAc]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, 9H, *J* = 7.2 Hz), 1.16 (d, 9H, *J* = 7.6 Hz), 1.33 (sept, 3H, *J* = 7.6 Hz), 1.50 – 1.88 (m, 8H), 2.46 – 2.51 (m, 1H), 2.58 (dt, 1H, *J* = 14.0, 8.4 Hz), 3.60 (dd, 1H, *J* = 12.0, 3.2 Hz), 4.92 (d, 1H, *J* = 10.0 Hz), 5.00 (d, 1H, *J* = 16.8 Hz), 5.09 – 5.14 (m, 1H), 5.70 – 5.82 (m, 1H), 8.11 (d, 2H, *J* = 8.4 Hz), 8.33 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 19.1, 23.8, 24.1, 32.2, 32.9, 33.2, 34.4, 82.2, 116.0, 124.1, 128.0, 137.4, 148.7, 149.9, 179.1; IR (film) cm^{-1} 2947m, 2871m, 1565s, 1531s, 1349s, 1303m, 1157s; mass spectrum (APCI): m/e (% relative intensity) 441 (30) $[M\text{-cyclopentene}+H]^+$; HRMS (ESI): m/e calcd for $C_{25}H_{40}N_2O_5SSiNa$ 531.2320, found 530.2333.

Imidate 4h—R_f = 0.30 [4:1 hexanes/EtOAc]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.59 (tt, 2H, *J* = 6.0, 1.2 Hz), 3.69 (s, 3H), 4.49 (t, 1H, 6.0 Hz), 5.10 (ddt, 1H, *J* = 10.4, 2.8, 1.6 Hz), 5.16 (ddt, 1H, *J* = 17.2, 2.8, 1.6 Hz), 5.72 (ddt, 1H, *J* = 17.2, 10.4, 6.0), 7.24 – 7.34 (m, 7H), 7.76 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 41.3, 45.8, 52.2, 117.7, 127.2, 127.3, 128.7, 129.4, 129.8, 133.2, 134.1, 137.1, 143.6, 172.2; IR (film) cm^{-1} 3034m, 2951m, 1735s, 1597m, 1325s; mass spectrum (APCI): m/e (% relative intensity) 344 (100) $[M+H]^+$; HRMS (ESI): m/e calcd for $C_{19}H_{21}NO_3SNa$ 366.1135, found 366.1150.

Imidate 4i—R_f = 0.48 [4:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, 3H, *J* = 7.0 Hz), 2.41 (s, 3H), 2.63 (dt, 1H, *J* = 13.5, 6.5 Hz) 2.83 (dt, 1H, *J* = 16.5, 8.0 Hz), 4.09 (dq, 1H, *J* = 11.0, 7.0 Hz), 4.19 (dq, 1H, *J* = 11.0, 7.0 Hz), 4.98 – 5.04 (m, 2H), 5.10 (dd, 1H, *J* = 17.0, 1.5 Hz), 5.70 – 5.80 (m, 1H), 7.23 – 7.28 (m, 3H), 7.32 (t, 2H, *J* = 8.0 Hz), 7.46 (d, 2H, *J* = 7.5 Hz), 7.77 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 21.7, 36.0, 37.9, 48.9, 64.6, 117.7, 126.9, 127.8, 128.8, 129.0, 129.5, 134.9, 137.8, 143.3, 174.6; IR (film) cm^{-1} 2985w, 1592s, 1301s, 1152s; mass spectrum (APCI): m/e (% relative intensity) 358 (100) $[M+H]^+$; HRMS (ESI): m/e calcd for $C_{20}H_{23}NO_3SNa$ 380.1291, found 380.1287.

Imidate 4j—R_f = 0.32 [6:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, 3H, *J* = 6.0 Hz), 1.25 (d, 3H, *J* = 6.5 Hz), 2.40 (s, 3H), 2.59 (dt, 1H, *J* = 12.5, 5.5 Hz), 2.80 (dt, 1H, *J* = 14.5, 8.5 Hz), 4.97 (m, 3H), 5.10 (d, 1H, *J* = 17.5 Hz), 5.70 – 5.79 (m, 1H), 7.22 – 7.27 (m, 3H), 7.31 (t, 2H, *J* = 7.5 Hz), 7.44 (d, 2H, *J* = 8.0 Hz), 7.75 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 21.4, 21.7, 38.1, 48.9, 72.5, 117.7, 126.8, 127.7, 128.7, 128.8, 129.5, 134.8, 137.9, 139.7, 143.1, 174.0; IR (film) cm^{-1} 2984w, 1592s, 1302s, 1156s; mass spectrum (APCI): m/e (% relative intensity) 330 (100) $[M\text{-propene}+H]^+$; HRMS (ESI): m/e calcd for $C_{21}H_{25}NO_3SNa$ 394.1448, found 394.1440.

Imidate 4k—R_f = 0.33 [4:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, 3H, *J* = 7.0 Hz), 2.62 (dt, 1H, *J* = 13.5, 7.0 Hz), 2.83 (dt, 1H, *J* = 15.5, 8.5 Hz), 3.84 (s, 3H), 4.09

(dq, 1H, *J* = 11.0, 7.0 Hz), 4.18 (dq, 1H, *J* = 11.0, 7.0 Hz), 4.99 – 5.04 (m, 2H), 5.09 (d, 1H, *J* = 17.0 Hz), 5.70 – 5.59 (m, 1H), 6.91 (d, 2H, *J* = 9.0 Hz), 7.26 (t, 1H, *J* = 7.5 Hz), 7.32 (d, 2H, *J* = 7.5 Hz), 7.45 (d, 2H, *J* = 7.5 Hz), 7.81 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 37.9, 48.8, 55.7, 64.8, 114.0, 117.7, 127.7, 128.8, 128.9, 128.9, 133.1, 134.9, 137.8, 162.9, 174.4; IR (film) cm^{-1} 2986w, 1593s, 1499m, 1298s, 1150s; mass spectrum (APCI): m/e (% relative intensity) 374 (100) $[M+H]^+$; HRMS (ESI): m/e calcd for $C_{20}H_{23}NO_4SNa$ 396.1231, found 396.1240.

Imidate 4l—R_f = 0.20 [4:1 hexanes/EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 – 1.83 (m, 8H), 2.59 (dt, 1H, *J* = 12.5, 6.5 Hz), 2.79 (dt, 1H, *J* = 17.0, 8.0 Hz), 3.85 (s, 3H), 4.99 (dd, 1H, *J* = 9.0, 7.0 Hz), 5.02 (d, 1H, *J* = 11.0 Hz), 5.09 (dd, 1H, *J* = 17.0, 1.5 Hz), 5.12 – 5.17 (m, 1H), 5.74 (dddd, 1H, *J* = 17.0, 10.0, 7.5, 5.5 Hz), 6.92 (d, 2H, *J* = 9.0 Hz), 7.24 – 7.28 (m, 1H), 7.31 (t, 2H, *J* = 7.0 Hz), 7.43 (d, 2H, *J* = 7.5 Hz), 7.81 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 32.4, 32.6, 38.0, 48.8, 55.8, 81.8, 114.0, 117.6, 127.7, 128.7, 128.8 128.8, 134.6, 134.9, 137.9, 162.7, 173.9; IR (film) cm^{-1} 2968w, 2850w, 1579s, 1294s, 1257s, 1150s; mass spectrum (APCI): m/e (% relative intensity) 346 (100) (M-cyclopentene+H)$^+$; HRMS (ESI): m/e calcd for $C_{23}H_{27}NO_4SNa$ 436.1553, found 436.1552.

Imidate 15—R_f = 0.50 [4:1 hexanes/EtOAc]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, 9H, *J* = 7.6 Hz), 1.17 (d, 9H, *J* = 7.6 Hz), 1.31 (sept, 3H, *J* = 7.6 Hz), 2.41 (s, 3H), 2.43 – 2.48 (m, 1H), 2.61 (td, 1H, *J* = 13.6, 8.8 Hz), 3.67 (dd, 1H, *J* = 12.0, 3.2 Hz), 4.47 (dd, 1H, *J* = 12.8, 6.0 Hz), 4.59 (dd, *J* = 12.8, 6.0 Hz), 4.87 (d, 1H, *J* = 10.0 Hz), 4.95 (d, 1H, *J* = 17.2 Hz), 5.22 (d, 1H, *J* = 10.4 Hz), 5.28 (dd, 1H, *J* = 16.0, 1.2 Hz), 5.63 – 5.74 (m, 1H), 5.87 (ddt, 1H, *J* = 16.8, 10.0, 6.0 Hz), 7.26 (d, 2H, *J* = 8.0 Hz), 7.80 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 19.1, 21.7, 32.5, 34.2, 69.1, 115.9, 119.8, 126.8, 126.9, 129.4, 131.6, 137.4, 140.1, 142.9, 177.4; IR (film) cm^{-1} 2943m, 2869m, 1584s, 1302m, 1155s; mass spectrum (APCI): m/e (% relative intensity) 450 (100) $[M+H]^+$; HRMS (ESI): m/e calcd for $C_{24}H_{39}NO_3SSiNa$ 472.2313, found 472.2305.

Synthesis of Amide 16

To a stirring solution of imidate **15** (35.0 mg, 0.078 mmol) in 1,2-dichloroethane (0.4 mL) was added $PdCl_2(PhCN)_2$ (1.5 mg, 0.004 mol). The reaction was stirred under a nitrogen atmosphere for 3 h at room temperature and then the solvent was removed by rotary evaporation. The crude residue was purified by flash silica gel column chromatography [isocratic eluent: 20:1 hexanes/EtOAc] to afford the amide **16** (35.0 mg, 0.078 mmol, >95% yield) as a colorless oil.

R_f = 0.50 [4:1 hexanes/EtOAc]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, 9H, *J* = 6.8 Hz), 1.11 (d, 9H, *J* = 6.8 Hz), 1.13 – 1.25 (m, 3H), 2.26 (dd, 1H, *J* = 11.6, 6.4 Hz), 2.43 (s, 3H), 2.66 (td, 1H, *J* = 13.2, 7.2 Hz), 3.00 (brs, 1H), 4.34 (dd, 1H, *J* = 16.4, 6.8 Hz), 4.47 – 4.54 (m, 1H), 4.69 (d, 1H, *J* = 10.0 Hz), 4.82 (d, 1H, *J* = 16.8 Hz), 5.21 (d, 1H, *J* = 10.0 Hz), 5.27 (d, 1H, *J* = 17.2 Hz), 5.21 – 5.37 (m, 1H), 7.29 (d, 2H, *J* = 8.8 Hz), 7.83 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.8, 19.2, 21.8, 34.8, 49.5, 116.0, 119.0, 128.0, 128.8, 129.5, 133.6, 137.4, 144.6, 176.0; IR (film) cm^{-1} 2950m, 2870m, 1678s, 1352s; mass spectrum (APCI): m/e (% relative intensity) 450 (100) $[M+H]^+$; HRMS (ESI): m/e calcd for $C_{24}H_{39}NO_3SSiNa$ 472.2313, found 472.2317.

Synthesis of Azapine-2-one 17

To a solution of amide **16** (35.0 mg, 0.078 mmol) in 1,2-dichloroethane was added Grubbs I catalyst (3.2 mg, 0.004 mmol). The reaction vial was flushed with dry nitrogen, sealed, and heated to 70 °C for 16 hours. The solvent was removed by rotary evaporation and the crude residue was purified by flash silica gel column chromatography [isocratic eluent: 10:1

hexanes/EtOAc] to afford azapine-2-one **17** (29.5 mg, 0.070 mmol, 90% yield) as a white solid.

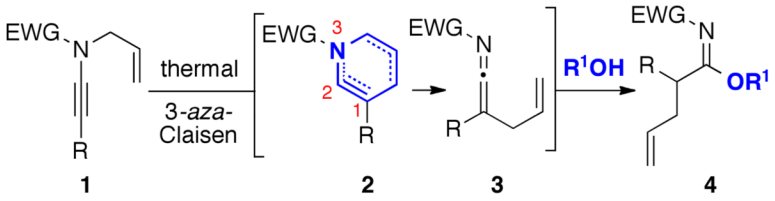
R_f = 0.30 [8:1 hexanes/EtOAc]; m.p. = 129 – 130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, 9H, *J* = 7.5 Hz), 0.99 (d, 9H, *J* = 7.5 Hz), 1.18 (sept, 3H, *J* = 7.5 Hz), 2.28 – 2.40 (m, 1H), 2.41 (s, 3H), 2.41 – 2.48 (m, 1H), 2.90 (dd, 1H, *J* = 13.0, 2.5 Hz), 4.49 (dt, 1H, *J* = 18.0, 3.0 Hz), 4.81 (dd, 1H, *J* = 18.0, 8.0 Hz), 5.75 – 5.79 (m, 1H), 5.83 – 5.88 (m, 1H), 7.26 (d, 2H, *J* = 8.0 Hz), 7.83 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (120 MHz, $CDCl_3$) δ 11.2, 19.3, 21.8, 28.1, 31.0, 43.1, 123.9, 128.5, 129.3, 133.6, 136.8, 144.3, 175.4; IR (film) cm^{-1} 2943m, 2866m, 1963s, 1597w, 1350s; mass spectrum (APCI): m/e (% relative intensity) 422 (100) $[M+H]^+$; HRMS (ESI): m/e calcd for $C_{22}H_{35}NO_3SSiNa$ 444.2000, found 444.2000.

References

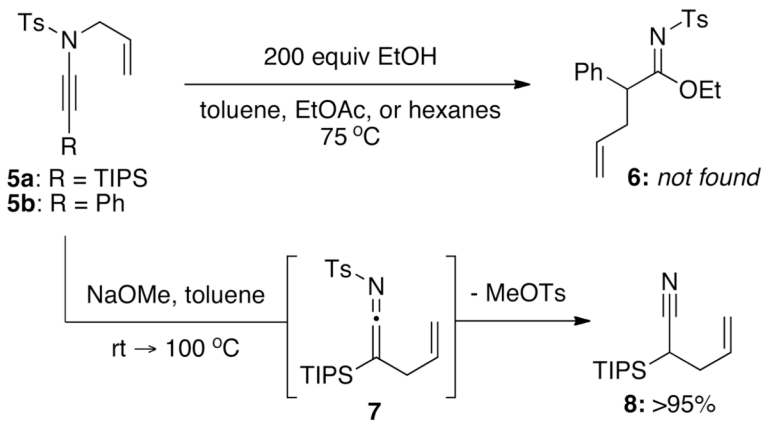
1. For reviews, see: (a) DeKorver KA, Li H, Lohse AG, Hayashi R, Lu Z, Zhang Y, Hsung RP. Chem Rev. 2010 ASAP. (b) Evano G, Coste A, Jouvin K. Angew Chem Int Ed 2010;49:2840.
2. For examples in 2010, see: (c) Li H, Antoline JE, Yang JH, Al-Rashid ZF, Hsung RP. New J Chem 2010;34 ASAP. (d) Kramer S, Madsen JLH, Rottländer M, Skrydstrup T. Org Lett 2010;12 ASAP. (e) Banerjee B, Litvinov DN, Kang J, Bettale JD, Castle SL. Org Lett 2010;12:2650. [PubMed: 20438051] (f) Gourdet B, Rudkin ME, Lam HW. Org Lett 2010;12:2554. [PubMed: 20446723] (g) Jia W, Jiao N. Org Lett 2010;12:2000. [PubMed: 20361747] (h) Burley GA, Davies DL, Griffith GA, Lee M, Singh K. J Org Chem 2010;75:980. [PubMed: 20047334] (i) Yamasaki R, Terashima N, Sotome I, Komagawa S, Saito S. J Org Chem 2010;75:480. [PubMed: 20014802]
3. Zhang Y, DeKorver KA, Lohse AG, Zhang YS, Huang J, Hsung RP. Org Lett 2009;11:899. [PubMed: 19199763]
4. DeKorver KA, Hsung RP, Lohse AG, Zhang Y. Org Lett 2010;12:1840. [PubMed: 20337418]
5. For leading reviews on aza-Claisen rearrangements, see: (a) Majumdar KC, Bhayyacharyya T, Chattopadhyay B, Nandi RK. Synthesis 2009:2117. (b) Nubbemeyer U. Top Curr Chem 2005;244:149.. For some examples of aza-Claisen rearrangements, see: (c) Majumdar KC, Samanta S, Chattopadhyay B, Nandi RK. Synthesis 2010:863. (d) Cheung LLW, Yudin AK. Org Lett 2009;11:1281. [PubMed: 19239262] (e) Cant AA, Bertrand GHV, Henderson JL, Roberts L, Greaney MF. Angew Chem Int Ed 2009;48:5199.
6. For reviews on the chemistry of ketenimines, see: (a) Krow GR. Angew Chem, Int Ed Engl 1971;10:435. (b) Gambaryan NP. Usp Khim 1976;45:1251. (c) Dondoni A. Heterocycles 1980;14:1547.(d) Barker, MW.; McHenry, WE. In The Chemistry of Ketenes, Allenes and Related Compounds. Patai, S., editor. Vol. Part 2. Wiley-Interscience; Chichester, UK: 1980. p. 701-720. (e) Alajarin M, Vidal A, Tovar F. Targets Heterocycl Syst 2000;4:293.
7. For examples of imidates serving as prodrugs, see: (a) Maryanoff BE, McComsey DF, Costanzo MJ, Yabut SC, Lu T, Player MR, Giardino EC, Damiano BP. Chem Biol Drug Des 2006;68:29. [PubMed: 16923023] (b) Poon SF, Stock N, Payne JE, McGuire AR, Stearns B, Yang X, Chen W, Munoz B, Smith ND. Bioorg Med Chem Lett 2005;15:2259. [PubMed: 15837305] (c) Bundgaard H, Drustrup Larsen J. J Med Chem 1988;31:2066. [PubMed: 3184119]
8. For recent examples of amidine formation, see: (a) Shang Y, He X, Hu J, Wu J, Zhang M, Yu S, Zhang Q. Adv Synth Catal 2009;351:2709. (b) She J, Jiang Z, Wang Y. Synlett 2009;12:2023. (c) Yu RT, Rovis T. J Am Chem Soc 2008;130:3262. [PubMed: 18302377] (d) Yoo EJ, Ahlquist M, Bae I, Sharpless B, Fokin V, Chang S. J Org Chem 2008;73:5520. [PubMed: 18557650]
9. For recent examples of imidate formation, see: (a) Song W, Lu W, Wang J, Lu P, Wang Y. J Org Chem 2010;75:3481. [PubMed: 20373817] (b) Yoo EJ, Park SH, Lee SH, Chang S. Org Lett 2009;11:1155. [PubMed: 19209900] (c) Yoo EJ, Bae I, Cho SH, Han H, Chang S. Org Lett 2006;8:1347–1350. [PubMed: 16562888]
10. For a recent example of α-functionalization of imidates, see: Matsubara R, Berthiol F, Kobayashi S. J Am Chem Soc 2008;130:1804–1805. [PubMed: 18198871]
11. For a related 1,3-shift, see: Bendikov M, Duong HM, Bolanos E, Wudl F. Org Lett 2005;7:783. [PubMed: 15727440]

12. (a) For leading references, see: Anderson CE, Overman LE. J Am Chem Soc 2003;125:12412. [PubMed: 14531676] . (b) For a review, see: Overman LE. Acc Chem Res 1980;13:218. Also see: (c) Overman LE. J Am Chem Soc 1974;96:597.. (d) Overman LE. J Am Chem Soc 1976;98:2901.

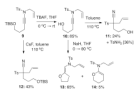
13. Tomooka K, Suzuki M, Uehara K, Shimada M, Akiyama T. Synlett 2008;16:2518.



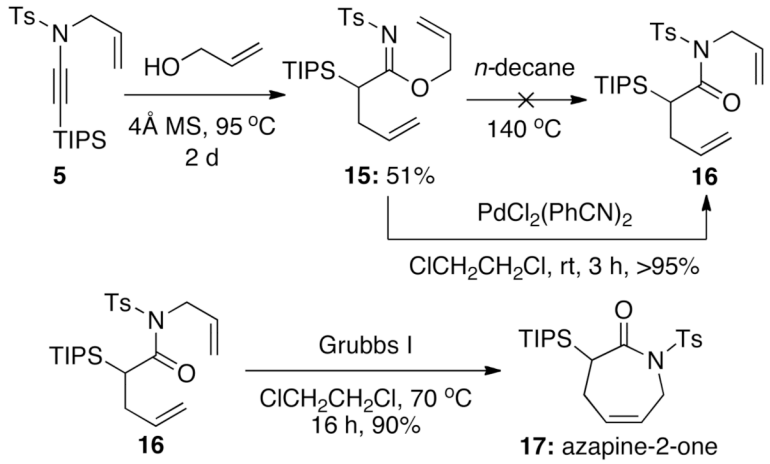
Scheme 1. In Situ Trapping of a Ketenimine Intermediate



Scheme 2. Alkoxide Induced Detosylation of the Ketenimine



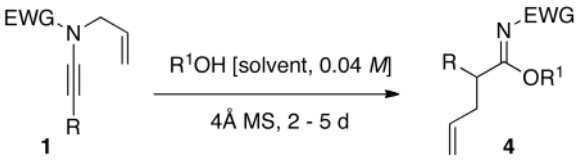
Scheme 3. Attempts at Intramolecular Imidate Formation

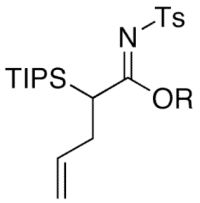
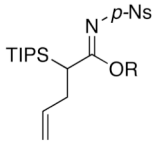
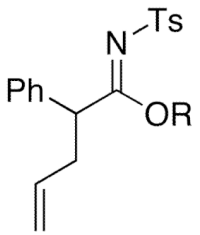
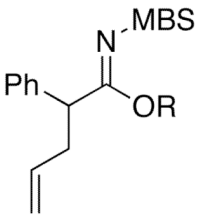


Scheme 4. Construction of an Azapine-2-one Scaffold

Table 1

Synthesis of α-Allyl Imidates



Entry	Alcohol	Temp/Time	Imidate	Yield [%][a]
1	MeOH	75 °C/2 d		**4a:** R = Me [81%]
2	EtOH	75 °C/2 d		**4b:** R = Et [43%]
3	*i*-PrOH	90 °C/5 d		**4c:** R = *i*-Pr [39%]
4	*c*-pentanol	110 °C/5 d		**4d:** R = *c*-pent [45%]
5	EtOH	85 °C/3 d		**4e:** R = Et [76%]
6	*i*-PrOH	90 °C/4 d		**4f:** R = *i*-Pr [76%]
7	*c*-pentanol	115 °C/4 d		**4g:** R = *c*-pent [71%]
8	MeOH	75 °C/2 d		**4h:** R = Me [95%][c]
9	EtOH	75 °C/2 d		**4i:** R = Et [75%]
10	*i*-PrOH	75 °C/5 d		**4j:** R = *i*-Pr [47%][d]
11	EtOH	75 °C/2 d		**4k:** R = Et [82%]
12	*c*-pentanol	75 °C/2 d		**4l:** R = *c*-pent [38%]

b

[a] Isolated Yields.

[b] MBS = *p*-methoxybenzenesulfonyl.

[c] No nitrile observed in crude ^{1}H NMR.

[d] Est. nitrile yield by crude ^{1}H NMR = 20%.