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A Silver(I)-Catalyzed Intramolecular Ficini's [2 + 2] Cycloaddition Employing Ynamides†

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Abstract

An intramolecular [2 + 2] cycloaddition using *N*-sulfonyl substituted ynamides tethered to an enone motif is described here. This thermally driven [2 + 2] cycloaddition manifold can be catalyzed effectively using AgNTf₂, and represents the first examples of an intramolecular Ficini reaction.

Keywords

Intramolecular [2 + 2] cycloaddition; ynamides; the Ficini reaction; AgNTf₂; and electrocyclic ring-opening

We reported the first examples of Ficini's [2 + 2] cycloaddition, or the Ficini reaction, employing ynamides in 2010 after a 13-year long attempt.¹ This final success came more than 40 years after Ficini^{2–5} had disclosed perhaps the most useful carbon-carbon bond forming reaction involving ynamines.^{2,6} The Ficini reaction³ entails a stepwise and thermally driven [2 + 2] cycloaddition⁷ of ynamines with α,β -unsaturated ketones, while our reaction¹ with ynamides **1** were promoted with Cu(II)/Ag(I) salts, leading to the formation of cyclobutenamides **3** via the proposed zwitter ionic intermediate **2** [Scheme 1]. Mezzetti⁸ subsequently reported a beautiful account of asymmetric Ficini [2 + 2] cycloadditions using a chiral dicationic Ru(II) complex. However, an intramolecular variant of the Ficini reaction has remained untapped using ynamides.⁹ Given that ynamides have become a powerful and

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versatile functional group in organic synthesis in the last 20 years,^{10,11} a successful intramolecular Ficini reaction using ynamides tethered with an enone motif as shown in **4** could prove to be a tantalizing possibility for constructing complex polycycles. We wish to communicate here our success in establishing the concept of an intramolecular [2 + 2] cycloaddition employing ynamides and its current limitations.

Our work commenced first with a new finding experimentally for the intermolecular [2 + 2] cycloaddition. We observed that it is not necessary to use both Cu(II) and Ag(I) catalysts to promote the intermolecular reaction. As shown in Table 1, the initial keys to render the [2 + 2] cycloaddition successful are that ynamides cannot be terminally unsubstituted as in **7** [entries 1 and 2], and that 20 mol% CuCl₂ and 60 mol% AbSbF₆ were found to be the most suitable catalytic system¹ to afford the desired cycloadduct **10** in high yield from ynamide **9** [entry 3]. However, our efforts post publication reveal that either Cu(II) or Ag(I) salt alone could catalyze this cycloaddition, and that silver is actually more superior. More specifically, AgNTf₂ in 10 mol% appears to be the best catalyst overall [entries 9 and 10]¹² in providing comparable outcome as those promoted by both CuCl₂ and AbSbF₆. While AgBF₄ also worked quite effectively [entry 6], the reaction took a much longer time [entries 6–8].

The discovery of Ag(I) catalyst proves out to be essential, as it turned out that the presence of 20 mol% CuCl₂ and 60 mol% AbSbF₆ were completely ineffective for the intramolecular [2 + 2] cycloaddition of ynamides **11a–d**.^{13–15} Consequently, we focused on the silver catalyst and quickly found that AgNTf₂ again was the best silver salt [entries 1–3 versus entry 4 in Table 2]. In addition, yields were better when the reaction was carried out in CH₂Cl₂ [entry 4 versus entries 6–9] and at higher concentrations [entries 4 and 12 versus entries 10 and 11].¹⁶ Lastly, the nature of the electron withdrawing group on the nitrogen atom did not appear to have a significant impact on the reaction [entry 4 versus entries 13–15].

Relative stereochemistry was assigned using nOe experiments performed using cycloadduct **12a** [Figure 1], and the scope of this cycloaddition is showcased in Figure 2. It is noteworthy that when the nitrogen atom is substituted with an alkene, yields of the cycloaddition are lower [see **13–16**]. This is likely due to competing complexation of the olefin with the silver catalyst followed by decomposition pathways. Only when there is sufficient distance between the olefin and the nitrogen atom, the cycloaddition could be improved [see **16**].

Unfortunately, when we turned to ynamide **20** in hope of obtaining cycloadduct **21**, we found instead only the half-cycloaddition product **22** after numerous attempts [Scheme 2]. While the relative stereochemistry is unassigned, isolation of **22** is most likely a result of direct hydrolysis of the zwitter ionic intermediate **23** after the first bond formation, although the desired cycloaddition could have taken place, and that a subsequent hydrolytic ring-opening of the desired cycloadduct **21** could lead to **22**. On the other hand, only when utilizing AgOTf as the catalyst, did we find the corresponding half-cycloaddition product **24** from ynamide **11a**. In all other cases, cycloadducts in which the cyclobutenamide is fused to a 6-membered ring could be prepared without problem. This distinct contrast suggests that

the ring strain in the anticipated cycloadduct **21**, where the cyclobutenamide is fused to a 5-membered ring, could be responsible in deterring the cycloaddition pathway.¹⁷

We then examined electrocyclic ring-opening of these [2 + 2] cycloadducts.¹⁸ As shown in Scheme 3, a highly torquoselective conrotatory ring-opening of cyclobutenamides **12a** and **12d** could take place effectively at 100 °C to afford 2-amidodienes **25a** and **25d**, respectively. Likewise, 2-amidodienes **26** and **27** could also be obtained in high yields from their respective starting cyclobutenamides **15** and **16**. The high level of torquoselectivity is predictably a result of the ring-junction hydrogen [in blue] rotating inwardly with respect to the cyclobutene ring to avoid the formation a *trans*-cyclohexene ring. This rotational preference trumps the inward rotation favored from the electron withdrawing carbonyl group based on Houk's prediction,¹⁹ and leads to the exclusive formation of *Z*-vinylogous amide, which was assigned using nOe experiments.

In addition, it is noteworthy that these 2-amidodienes favor the *S*-*trans* conformation with *E* being 4.03 kcal mol⁻¹ for **25a** from B3LYP/6-31G* [SpartanTM] calculations. Such conformational preference for *S*-*trans* is likely to avoid allylic strain. Consequently, our preliminary attempts to carry out an obvious application in the form of [4 + 2] cycloadditions were not successful using 2-amidodienes **26** and **27**, with the latter as an attempt for a possible intramolecular [4 + 2] cycloaddition.²⁰ We are currently exploring other possible applications that can distinctly showcase synthetic potential of these highly functionalized unique dienes.

We have described here an intramolecular [2 + 2] cycloaddition using *N*-sulfonyl substituted ynamides tethered to an enone motif. This intramolecular Ficini reaction could be effectively catalyzed using AgNTf₂. Our work represents the first examples of an intramolecular variant of Ficini's original ynamine-[2 + 2] cycloaddition. Efforts are underway in further development of this new cycloaddition and its applications.

Acknowledgments

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16. **Selected Experimental Details and Characterizations.** To a flame-dried screw-cap vial containing AgNTf₂ (3.1 mg, 0.016 mmol) was added a solution of 11a (64.8 mg, 0.16 mmol) in CH₂Cl₂ (1.0 mL) at rt under N₂. The reaction was stirred at rt for 3 h and monitored by TLC. When all the starting material was consumed, the solvent was removed under reduced pressure. The resulting crude mixture was purified by flash silica gel column chromatography [isocratic eluent: 8:1 hexanes/EtOAc + 3% Et₃N] to afford cyclobutenamide 12a (37.5 mg, 0.092 mmol, 58% yield) as a colorless oil. **12a:** R_f = 0.13 [8:1 Hexane/EtOAc]; ¹H NMR (400 MHz, CDCl₃) δ 0.68–0.78 (m, 1H), 0.83–0.92 (m, 1H), 1.07–1.17 (m, 1H), 1.58–1.61 (m, 2H), 1.68–1.75 (m, 1H), 1.97 (s, 3H), 2.00–2.13 (m, 3H), 2.44 (s, 3H), 3.41 (d, 1H, *J* = 1.2 Hz), 4.41 (d, 1H, *J* = 15.2 Hz), 4.66 (d, 1H, *J* = 15.2 Hz), 7.23–7.33 (m, 7H), 7.73 (d, 2H, *J* = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.7, 24.4, 25.8, 25.9, 28.4, 32.1, 39.8, 52.1, 62.8, 125.0, 127.5, 127.8, 127.9, 128.6, 129.8, 136.3, 136.5, 139.9, 143.9, 208.1; IR (film) cm⁻¹ 2928brm, 2851w, 2362w, 1704s, 1353s, 1163s; mass spectrum (APCI): *m/e* (% relative intensity) 410 (100) (M+H)⁺. **12b:** R_f = 0.29 [3:1 Hexane/EtOAc]; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 0.68–0.79 (m, 1H), 0.83–0.93 (m, 1H), 1.06–1.18 (m, 1H), 1.57–1.62 (m, 2H), 1.68–1.76 (m, 1H), 1.99 (s, 3H), 1.99–2.13 (m, 3H), 3.42 (d, 1H, *J* = 1.6 Hz), 3.87 (s, 3H), 4.42 (d, 1H, *J* = 15.2 Hz), 4.64 (d, 1H, *J* = 15.2 Hz), 6.97–7.00 (m, 2H), 7.24–7.33 (m, 5H), 7.77–7.80 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 24.4, 25.8, 25.9, 28.4, 32.1, 39.9, 52.0, 55.8, 62.7, 114.3, 125.1, 127.7, 127.8, 127.9, 128.6, 129.7, 131.1, 136.3, 139.3, 163.2, 208.1; IR (film) cm⁻¹ 2932brm, 2849w, 1704m, 1596m, 1497m, 1353s, 1260s, 1159s; mass spectrum (APCI): *m/e* (% relative intensity) 426 (41) (M+H)⁺. **12c:** R_f = 0.22 [8:1 Hexane/EtOAc]; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 0.65–0.77 (m, 1H), 0.81–0.91 (m, 1H), 1.08–1.23 (m, 1H), 1.59–1.62 (m, 2H), 1.69–1.77 (m, 1H), 2.01 (s, 3H), 2.03–2.13 (m, 3H), 3.41 (d, 1H, *J* = 1.6 Hz), 4.45 (d, 1H, *J* = 15.2 Hz), 4.64 (d, 1H, *J* = 15.2 Hz), 7.24–7.34 (m, 5H), 7.61–7.73 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 24.3, 25.7, 25.9, 28.6, 32.1, 40.1, 52.1, 62.5, 124.5, 127.8, 127.9, 128.0, 128.7, 129.1, 132.4, 136.0, 138.5, 140.0, 207.8; IR (film) cm⁻¹ 2932brm, 2853w, 1705s, 1357s, 1168s; mass spectrum (APCI): *m/e* (% relative intensity) 474 (100) (M+H)⁺. **12d:** R_f = 0.42 [3:1 Hexane/EtOAc]; pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 0.65–0.75 (m, 1H), 0.82–0.92 (m, 1H), 1.06–1.19 (m, 1H), 1.60–1.64 (m, 2H), 1.73–1.80 (m, 1H), 2.40 (s, 3H), 2.05–2.15 (m, 3H), 3.42 (d, 1H, *J* = 1.2 Hz), 4.51 (d, 1H, *J* = 15.2 Hz), 4.69 (d, 1H, *J* = 15.2 Hz), 7.26–7.34 (m, 5H), 8.01–8.04 (m, 2H), 8.33–8.36 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 24.3, 25.8, 26.0, 28.8, 32.2, 40.6, 52.2, 62.3, 123.9, 124.3, 127.7, 128.1, 128.8, 128.9, 135.6, 140.3, 145.3, 150.3, 207.5; IR (film) cm⁻¹ 2934brm, 2854w, 1706m, 1531s, 1350s, 1169s; mass spectrum (ESI): *m/e* (% relative intensity) 458 (100) (M+NH₄)⁺; HRMS (ESI): *m/z* calcd for C₂₃H₂₈N₃O₅S [M+NH₄]⁺: 458.1745, found 458.1759. **13:** R_f = 0.28 [3:1 Hexane/EtOAc]; colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 0.97–1.10 (m, 2H), 1.18–1.26 (m, 1H), 1.69–1.71 (m, 2H), 1.83–1.88 (m, 1H), 2.10–2.20 (m, 3H), 2.14 (s, 3H), 2.43 (s, 3H), 3.55 (s, 3H), 3.82 (dd, 1H, *J* = 16.0, 5.5 Hz), 4.11 (dd, 1H, *J* = 15.5, 4.0 Hz), 5.14–5.22 (m, 2H), 5.74–5.82 (m, 1H), 7.31 (d, 2H, *J* = 8.0 Hz), 7.71 (d, 2H, *J* = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.7, 24.5, 26.06, 26.08, 28.8, 32.2, 40.1, 51.0, 62.6, 118.0, 125.1, 127.6, 129.7, 133.0, 136.4, 137.9, 143.9, 208.2; IR (film) cm⁻¹ 2933brm, 2853w, 2254w, 1704s, 1356s, 1165s; mass spectrum (APCI): *m/e* (% relative intensity) 360 (100) (M+H)⁺. **14:** R_f = 0.55 [3:1 Hexane/EtOAc]; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 0.94–1.05 (m, 2H), 1.15–1.23 (m, 1H), 1.52–1.73 (m, 8H), 1.80–1.89 (m, 1H), 1.97–1.99 (m, 2H), 2.10 (s, 3H), 2.07–2.26 (m, 3H), 2.42 (s, 3H), 3.49 (d, 1H, *J* = 1.2 Hz), 3.69 (d, 1H, *J* = 14.8 Hz), 3.92 (d, 1H, *J* = 14.8 Hz), 5.55 (t, 1H, *J* = 1.6 Hz), 7.29–7.31 (m, 2H), 7.68–7.71 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.7, 22.5, 22.6, 24.6, 25.3, 26.10, 26.14, 28.7, 32.3, 39.6, 54.6, 62.8, 125.4, 125.5, 127.6, 129.7, 132.4, 136.6, 139.4, 143.7, 208.4, one carbon missing due to overlap; IR (film) cm⁻¹ 2932brm, 2851w, 1709s, 1354s, 1166s; mass spectrum (APCI): *m/e* (% relative intensity) 414 (100) (M+H)⁺. **15:** R_f = 0.45 [3:1 Hexane/EtOAc]; colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 0.88–1.12 (m, 2H), 1.19–1.28 (m, 1H), 1.70–1.75 (m, 2H), 1.87–1.93 (m, 1H), 2.10–2.13 (m, 3H), 2.17 (s, 3H), 2.20–2.24 (m, 1H), 2.33–2.45 (m, 2H), 2.43 (s, 3H), 3.20 (ddd, 1H, *J* = 14.0, 8.5, 6.0 Hz), 3.51 (ddd, 1H, *J* = 15.5, 8.5, 5.8 Hz), 3.59 (d, 1H, *J* = 1.0 Hz), 5.04–5.10 (m, 2H), 5.75 (ddt, 1H, *J* = 17.5, 10.5, 6.7 Hz), 7.31 (d, 2H, *J* = 7.5 Hz), 7.70 (d, 2H, *J* = 8.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 21.7, 24.6, 25.8, 26.0, 29.2, 32.1, 33.0, 34.0, 48.0, 62.6, 117.4, 125.4, 127.5, 129.8, 134.5, 136.3, 138.1, 143.8, 208.2; IR

(film) cm^{-1} 2931brm, 2853w, 2254w, 2358w, 1707s, 1355s, 1164s; mass spectrum (ESI): m/e (% relative intensity) 391 (100) ($\text{M}+\text{NH}_4$)⁺; HRMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{28}\text{NO}_3\text{S}$ [$\text{M}+\text{H}$]⁺: 374.1785, found 374.1781. **16**: R_f = 0.17 [8:1 Hexane/EtOAc]; yellow oil; ¹H NMR (400 MHz, CDCl_3) δ 1.01–1.14 (m, 2H), 1.22–1.31 (m, 2H), 1.71–1.82 (m, 4H), 1.83–2.00 (m, 1H), 2.10–2.24 (m, 4H), 2.16 (s, 3H), 3.17–3.24 (m, 1H), 3.42–3.49 (m, 1H), 3.59 (s, 1H), 4.99–5.07 (m, 2H), 5.78 (ddt, 1H, J = 17.2, 10.4, 6.8 Hz), 8.02 (d, 2H, J = 8.8 Hz), 8.37 (d, 2H, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl_3) δ 24.4, 25.8, 26.1, 27.8, 29.2, 30.6, 32.3, 40.5, 48.3, 62.1, 115.8, 124.1, 124.3, 128.6, 137.2, 139.1, 144.9, 150.2, 207.3; IR (film) cm^{-1} 2930brm, 2852w, 1707s, 1530s, 1349s, 1167s; mass spectrum (ESI): m/e (% relative intensity) 436 (100) ($\text{M}+\text{NH}_4$)⁺; HRMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_5\text{S}$ [$\text{M}+\text{H}$]⁺: 419.1636, found 419.1640. **17**: R_f = 0.51 [3:1 Hexane/EtOAc]; colorless oil; ¹H NMR (400 MHz, CDCl_3) δ 1.04 (s, 9H), 1.07–0.9 (m, 2H), 1.16–1.27 (m, 2H), 1.68–1.71 (m, 2H), 1.80–1.98 (m, 3H), 2.09–2.20 (m, 3H), 2.14 (s, 3H), 2.42 (s, 3H), 3.25–3.32 (m, 1H), 3.57–3.64 (m, 2H), 3.69 (t, 2H, J = 5.8 Hz), 7.29 (d, 1H, J = 8.0 Hz), 7.35–7.44 (m, 6H), 7.62–7.68 (m, 4H), 7.69 (d, 2H, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl_3) δ 19.3, 21.7, 24.6, 25.8, 26.1, 27.0, 29.0, 31.5, 32.1, 40.0, 46.1, 61.4, 62.4, 125.5, 127.5, 127.8, 129.7, 129.8, 133.67, 133.73, 135.67, 135.69, 143.7, 208.1; IR (film) cm^{-1} 2932brm, 2857w, 1704m, 1356s, 1165s, 1110s, 1090s; mass spectrum (ESI): m/e (% relative intensity) 633 (100) ($\text{M}+\text{NH}_4$)⁺; HRMS (ESI): m/z calcd for $\text{C}_{36}\text{H}_{49}\text{N}_2\text{O}_4\text{SSi}$ [$\text{M}+\text{NH}_4$]⁺: 633.3177, found 633.3170. **18**: R_f = 0.18 [8:1 Hexane/EtOAc]; colorless oil; ¹H NMR (400 MHz, CDCl_3) δ 0.85–0.95 (m, 1H), 1.07–1.19 (m, 2H), 1.56–1.67 (m, 3H), 1.91–1.96 (m, 1H), 2.10–2.22 (m, 1H), 2.40 (s, 3H), 4.27 (s, 1H), 4.57 (s, 2H), 7.24–7.34 (m, 7H), 7.41–7.45 (m, 2H), 7.52–7.56 (m, 1H), 7.76 (d, 2H, J = 8.4 Hz), 7.83–7.85 (m, 2H); ¹³C NMR (100 MHz, CDCl_3) δ 21.7, 24.5, 25.6, 25.9, 32.2, 41.4, 52.4, 58.2, 124.8, 127.6, 127.7, 128.2, 128.4, 128.5, 128.6, 129.7, 133.1, 136.8, 137.0, 141.1, 143.6, 198.5, one carbon missing due to overlap; IR (film) cm^{-1} 2927brm, 2852w, 1679s, 1352s, 1164s; mass spectrum (APCI): m/e (% relative intensity) 472 (100) ($\text{M}+\text{H}$)⁺. **19**: R_f = 0.17 [1:1 Hexane/EtOAc]; pale yellow oil; ¹H NMR (400 MHz, CDCl_3) δ 0.72–0.91 (m, 1H), 0.95 (s, 3H), 1.12 (s, 3H), 1.07–1.17 (m, 1H), 1.56–1.59 (m, 2H), 1.67–1.73 (m, 1H), 1.98–2.01 (m, 1H), 2.12 (s, 3H), 2.18–2.24 (m, 2H), 3.35 (s, 1H), 3.84–3.93 (m, 2H), 4.22 (d, 1H, J = 6.4 Hz), 4.24 (d, 1H, J = 6.8 Hz), 4.38 (dd, 1H, J = 16.0, 10.4 Hz), 4.64 (dd, 1H, J = 16.0, 10.4 Hz), 7.23–7.43 (m, 6H); ¹³C NMR (100 MHz, CDCl_3) δ 21.2, 22.1, 24.6, 25.4, 25.8, 28.0, 32.18 (d, J = 6.1 Hz), 32.2, 39.9, 50.3 (d, J = 4.5 Hz), 61.4 (d, J = 2.3 Hz), 76.7 (d, J = 5.4 Hz), 126.5, 126.6, 127.3, 127.4, 128.5, 137.8 (d, J = 2.3 Hz), 208.6; ³¹P NMR (162 MHz, CDCl_3) δ 2.47; IR (film) cm^{-1} 2930brm, 1704s, 1326m, 1281m, 1254m, 1054s; mass spectrum (APCI): m/e (% relative intensity) 404 (100) ($\text{M}+\text{H}$)⁺. To a flamed-dried sealed tube was added a solution of cyclobutenamide **12a** (18.3 mg, 0.045 mmol) in toluene (1.0 mL). The resulting solution was heated at 100 °C for 2 h. The crude mixture was purified using silica gel flash column chromatography [gradient eluent: Hexanes to 8:1 Hexane/EtOAc] to afford amido-diene **25a** (17.3 mg, 0.042 mmol) in 95% yield. **25a**: R_f = 0.34 [3:1 Hexane/EtOAc]; pale yellow oil; ¹H NMR (400 MHz, CDCl_3) δ 1.42–1.45 (m, 2H), 1.53–1.55 (m, 2H), 1.89–1.90 (m, 4H), 2.01 (s, 3H), 2.43 (s, 3H), 4.63 (s, 2H), 5.84 (s, 1H), 6.03 (s, 1H), 7.24–7.34 (m, 7H), 7.72 (d, 2H, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl_3) δ 21.6, 21.7, 22.6, 26.3, 26.4, 31.3, 54.5, 122.6, 128.1, 128.3, 129.5, 130.3, 134.0, 135.8, 137.2, 137.5, 143.6, 147.3, 196.9, one carbon missing due to overlap; IR (film) cm^{-1} 2925brm, 2855w, 1692w, 1597w, 1572w, 1351m, 1160s; mass spectrum (ESI): m/e (% relative intensity) 427 (100) ($\text{M}+\text{NH}_4$)⁺; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_3\text{S}$ [$\text{M}+\text{NH}_4$]⁺: 427.2050, found 427.2051. **25d**: R_f = 0.36 [3:1 Hexane/EtOAc]; pale yellow oil; ¹H NMR (400 MHz, CDCl_3) δ 1.42–1.45 (m, 2H), 1.53–1.59 (m, 2H), 1.92–1.96 (m, 4H), 2.02 (s, 3H), 4.67–4.70 (m, 2H), 6.02 (t, 1H, J = 4.0 Hz), 6.12 (s, 1H), 7.21–7.28 (m, 5H), 7.94–7.97 (m, 2H), 8.29–8.33 (m, 2H); ¹³C NMR (100 MHz, CDCl_3) δ 21.5, 22.5, 26.2, 26.5, 32.0, 55.4, 120.7, 124.0, 128.37, 128.44, 129.2, 130.4, 134.3, 135.1, 139.1, 146.4, 147.6, 150.1, 195.8; IR (film) cm^{-1} 2929brm, 2860w, 1688w, 1571w, 1529s, 1349s, 1163s; mass spectrum (ESI): m/e (% relative intensity) 458 (100) ($\text{M}+\text{NH}_4$)⁺; HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_5\text{S}$ [$\text{M}+\text{H}$]⁺: 441.1479, found 441.1492. **26**: R_f = 0.14 [8:1 Hexane/EtOAc]; colorless oil; ¹H NMR (500 MHz, CDCl_3) δ 1.55–1.57 (m, 2H), 1.65–1.67 (m, 2H), 2.07–2.08 (m, 4H), 2.19 (s, 3H), 2.33–2.38 (m, 2H), 2.42 (s, 3H), 3.44–3.47 (m, 2H), 4.99–5.05 (m, 2H), 5.69 (ddt, 1H, J = 17.0, 10.5, 6.5 Hz), 6.05 (s, 1H), 6.14 (s, 1H), 7.26 (d, 2H, J = 8.0 Hz), 7.66 (d, 2H, J = 8.0 Hz); ¹³C NMR (125 MHz, CDCl_3) δ 21.7, 21.8, 22.6, 26.4, 26.5, 31.5, 33.7, 50.7, 117.0, 122.7, 128.0, 129.5, 134.3, 135.0, 136.5, 137.2, 143.5, 147.3, 196.8; IR (film) cm^{-1} 2926brm, 2858w, 1693m, 1597m, 1349s, 1161s; mass spectrum (ESI): m/e (% relative intensity) 458 (100) ($\text{M}+\text{NH}_4$)⁺.

relative intensity) 374 (100) (M+NH₄)⁺; HRMS (ESI): *m/z* calcd for C₂₁H₂₈NO₃S [M+H]⁺: 374.1785, found 374.1785. **27**: R_f = 0.18 [8:1 Hexane/EtOAc]; pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 1.58–1.75 (m, 6H), 2.01 (q, 2H, *J* = 7.1 Hz), 2.09 (s, 3H), 2.17–2.20 (m, 4H), 3.42 (m, 2H), 4.96–5.02 (m, 2H), 5.73 (ddt, 1H, *J* = 17.2, 10.4, 6.8 Hz), 6.18 (s, 1H), 6.35 (t, 1H, *J* = 4.0 Hz), 7.94 (d, 2H, *J* = 9.2 Hz), 8.31 (d, 2H, *J* = 9.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.7, 22.6, 26.5, 26.6, 28.2, 31.1, 32.1, 51.5, 115.6, 120.7, 124.0, 129.1, 135.1, 137.4, 137.8, 146.0, 147.6, 150.1, 195.7; IR (film) cm⁻¹ 2933brm, 2862w, 1691m, 1572m, 1530s, 1350s, 1164s; mass spectrum (ESI): *m/e* (% relative intensity) 436 (100) (M+NH₄)⁺; HRMS (ESI): *m/z* calcd for C₂₁H₂₇N₂O₅S [M+H]⁺: 419.1636, found 419.1637.

17. Attempted to synthesize ynamide in which the tethering contains a heteroatom failed.
18. Wang XN, Krenske EK, Johnston RC, Houk KN, Hsung RP. J Am Chem Soc. 2014; 136:9802. [PubMed: 24992255]
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20. For our recent work on [4 + 2] cycloadditions using 2-amidodienes, see:(a) Fang LC, Hsung RP. Organic Lett. 2014; 16:1826.(b) Fang LC, Hsung RP, Ma ZX, Presser WR. Organic Lett. 2013; 15:4842.

Figure 1.
Stereochemical Assignment of **12a** via nOe Experiment.

Figure 2.
Scope of the Intramolecular Cycloaddition.

Scheme 1.
Ficini's [2 + 2] Cycloaddition Using Ynamides.

Scheme 2.
Observations of the Half-Cycloaddition Products.

Scheme 3.

Pericyclic Ring-Opening of the [2 + 2] Cycloadducts.

The Effectiveness of Silver Salts.

Table 1

entry	R	solvent	catalyst [mol %]	temp [°C]	time [h] ^a	yield [%] ^b
1	7 : H	CH ₃ CN	AgSbF ₆ [10]	0 to 80	5	0 ^c
2	7 : H	CH ₂ Cl ₂	CuCl ₂ /AgSbF ₆ [20/42]	-78 to rt	10	5 ^d
3	9 : Me	CH ₂ Cl ₂	CuCl ₂ /AgSbF ₆ [20/60]	0	1	83
4	9 : Me	CH ₂ Cl ₂	Cu(OTf) ₂ [10] ^e	rt	3	53
5	9 : Me	CH ₂ Cl ₂	AgOAc [10] ^e	rt	48	NR
6	9 : Me	CH ₂ Cl ₂	AgBF ₄ [10] ^e	rt	3	91
7	9 : Me	CH ₂ Cl ₂	AgBF ₄ [10]	rt	3	13
8	9 : Me	CH ₂ Cl ₂	AgBF ₄ [20]	rt	3	21
9	9 : Me	CH ₂ Cl ₂	AgNTf ₂ [10] ^e	rt	3	88
10	9 : Me	CH ₂ Cl ₂	AgNTf ₂ [10]	rt	3	79
11	9 : Me	CH ₂ Cl ₂	AgSbF ₆ [10]	rt	3	45

^aTime for syringe pump addition of a solution of ynamide **7** or **9** and enone to the catalyst mixture.^bIsolated yields.^cNo reaction – recovered starting material **7**.^dPolymerization was the major outcome in addition to hydrolysis.^eThese reactions were run without 4Å MS.

Table 2

A Ag(I)-Catalyzed Intramolecular Cycloaddition.

entry	ynamides	EWG =	catalyst	solvent	concn [M]	cycloadducts	yield [%] ^a
1	11a	Ts	AgSbF ₆	CH ₂ Cl ₂	0.158	12a	32
2	11a	Ts	AgOTf	CH ₂ Cl ₂	0.158	12a	0
3	11a	Ts	AgBF ₄	CH ₂ Cl ₂	0.158	12a	52
4	11a	Ts	AgNTf ₂	CH ₂ Cl ₂	0.158	12a	58
5	11a	Ts	AgNTf ₂	CH ₂ Cl ₂	0.158	12a	0 ^b
6	11a	Ts	AgNTf ₂	DMF	0.158	12a	— ^c
7	11a	Ts	AgNTf ₂	THF	0.158	12a	11
8	11a	Ts	AgNTf ₂	Et ₂ O	0.158	12a	34
9	11a	Ts	AgNTf ₂	Toluene	0.158	12a	23
10	11a	Ts	AgNTf ₂	CH ₂ Cl ₂	0.0158	12a	26
11	11a	Ts	AgNTf ₂	CH ₂ Cl ₂	0.0316	12a	27
12	11a	Ts	AgNTf ₂	CH ₂ Cl ₂	0.316	12a	52
13	11b	Mbs	AgNTf ₂	CH ₂ Cl ₂	0.158	12b	55
14	11c	Bs	AgNTf ₂	CH ₂ Cl ₂	0.158	12c	60
15	11d	Ns	AgNTf ₂	CH ₂ Cl ₂	0.158	12d	33

^a Isolated yields.^b Using 4 Å MS; no reaction observed with recovery of **11a**.^c No reaction with decomposition.