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Silver-Catalyzed Cyclization of Propargylic Amides to Oxazolines

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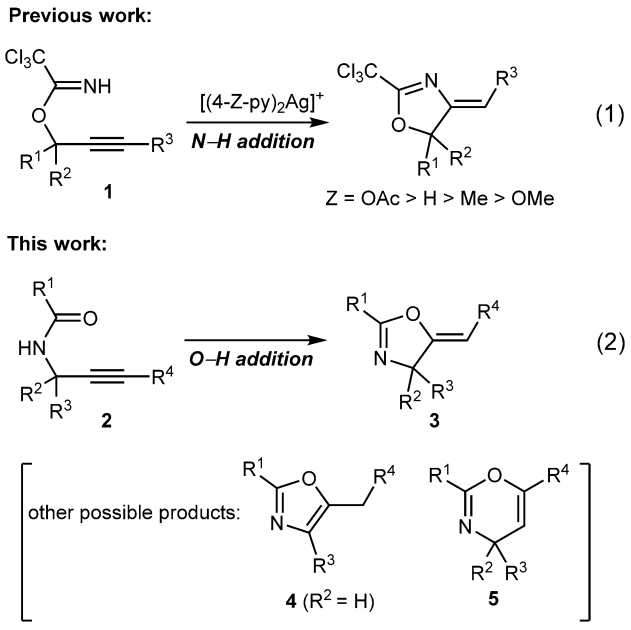
Abstract: A ligand-accelerated effect is observed in the cyclization of propargylic amides catalyzed by bis(pyridyl)silver(I) complexes, with an unexpected reversal of electronic demand to the analogous N–H addition reaction. The catalyst was found to be effective for internal alkyne substrates, offering exclusive selectivity for the 5-*exo-dig* product. Differences in selectivity profile between gold- and silver-catalyzed processes are highlighted and discussed.

Keywords: cyclization; heterocycles; oxazolines; silver

Introduction

Previously, we have reported the catalytic activity of bis(pyridyl)silver(I) complexes for the intramolecular cyclization of *O*-propargyl imidates **1** [Scheme 1, Eq. (1)].[1a] The cyclization proceeds exclusively with 5-*exo-dig* selectivity, to generate 2-oxazolines containing a methylene unit at C-4. More recently in this journal, we revealed that the rate of this reaction is highly sensitive to the ligand's electronic properties; the reaction rate was greatly enhanced by electron-withdrawing groups on pyridine.[1b] These results encouraged us to initiate a study to investigate the utility of these silver complexes in the cyclization of propargylic amides **2**, which is a highly complementary strategy, in that the heteroatoms on the acyclic substrate are interchanged [Scheme 1, Eq. (2)], producing the heterocycle *via* a formal O–H addition process.



Scheme 1. Synthesis of 2-oxazolines by complementary intramolecular N–H or O–H addition reactions.

A number of catalysts have been reported for this type of cyclization, including simple acid, base and non-precious metals.[2] However, the reaction conditions are rather impractical, requiring very high catalyst loadings, stoichiometric reagents, and/or elevated temperatures. In terms of the coinage metals, simple CuI[3] and $AgSbF_6$[4] salts have been reported to mediate 5-*exo-dig* cyclization reactions, but are only effective for substrates containing geminal substituents at the propargylic position (R^2 and R^3 = alkyl); presumably assisted by the Thorpe–Ingold effect. In comparison, gold catalysts have a much wider scope, and exhibit different selectivity profiles, depending on the oxidation state and ligand. In the presence of $AuCl_3$, cyclization of terminal alkyne substrates (R^4 = H) gave aromatic oxazoles **4** as the primary product,[5] while the use of cationic Au(I)-phosphine complexes promoted the formation of oxazolines **3**.[6]

In terms of substrate scope, cyclization of internal alkynes (where $R^4 \neq H$) is rare. To date, this is only possible by using a stoichiometric amount of acid in refluxing toluene to afford oxazole **3**,[2b] or by using

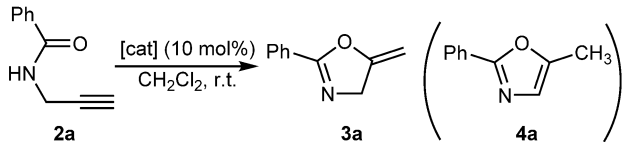
N-heterocyclic carbene (NHC) complexes of Au, to furnish either the oxazoline **3**, or the 6-*endo-dig* product **5**, depending on the substituents present.[7] In this article, we report a ligand-assisted silver-catalyzed process for the intramolecular cyclization of propargylic amide substrates under ambient conditions, which offers exclusive selectivity for the 5-*exo-dig* products **3**.

Results and Discussion

To avoid biases by Thorpe–Ingold and thermal effects, the optimization studies were performed at ambient temperature, using the simple, unsubstituted propargylic amide **2a** in a solution of CH_2Cl_2 (selected examples presented in Table 1, see also Table S1 in the Supporting Information). Guided by our previous study, the activity of electronically different silver(I) bis(pyridyl) triflate complexes was assessed (entries 1–5). In this case, an increase in catalyst efficiency is associated with more *electron-rich* pyridyl ligands, with 4-methoxypyridine offering the best performance (entry 4). Catalyst deactivation was indicated by the formation of insoluble white precipitates during the reaction; this was most severe with the DMAP complex, which is catalytically inactive (entry 5). This result is surprising as the reverse trend was observed in the previous study of the analogous N–H addition [Scheme 1, Eq. (1)]; where the most electron-deficient 4-Ac-Py offered the highest catalytic activity.[1b] This implies that different turnover-limiting steps operate in the N–H and O–H addition reactions to alkynes catalyzed by silver. The optimization study concluded with an investigation of the counter anion effect (entries 6–10), where the slightly coordinating TfO^- and $CF_3CO_2^-$ (entries 4 and 10) were much less productive than the non-coordinating PF_6^-, BF_4^- and SbF_6^- counter anions, which afforded near quantitative yields of **3a** (entries 9 and 10) at half the catalyst loading.

Subsequently, the cyclization of sixteen substrates containing different substituents at the amide (R^1), propargylic positions (R^2 and R^3) and alkyne (R^4) were examined (Figure 1). In all cases, only the non-aromatic 5-*exo-dig* products (**3**) were obtained. Alkyl, aryl and crotonyl substituents were well tolerated as the amide substituent (R^1), affording **3a**–**3d** in good conversions. Vinyl (**2e**) and ethoxy (**2f**) substituents at R^1 afforded low conversions of unidentifiable products, while no reaction was observed for the ester-sub-

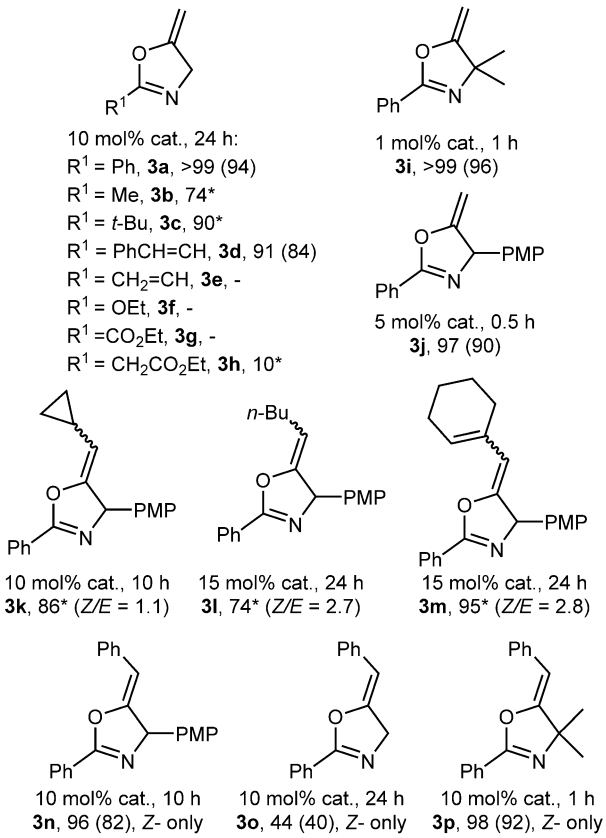
Table 1. Initial reaction optimization.[a]



2a 3a 4a

Entry	[Cat]	mol%	Time [h]	Yield[b] [%]
1	$[(Py)_2Ag]OTf$	10	6	8
2	$[(4\text{-Ac-Py})_2Ag]OTf$	10	6	26
3	$[(4\text{-Me-Py})_2Ag]OTf$	10	6	59
4	$[(4\text{-MeO-Py})_2Ag]OTf$	10	6	85
5	$[(4\text{-NMe2-Py})_2Ag]OTf$	10	6	5
6	$[(4\text{-MeO-Py})_2Ag]ClO_4$	10	6	98
7	$[(4\text{-MeO-Py})_2Ag][TFA]$	10	6	31
8	$[(4\text{-MeO-Py})_2Ag]BF_4$	5	24	93
9	$[(4\text{-MeO-Py})_2Ag]PF_6$	5	24	96
10	$[(4\text{-MeO-Py})_2Ag]SbF_6$	5	24	95

[a] *Reaction conditions:* substrate **2a** (0.4 mmol), catalyst (0.04 mmol, 10 mol%), 23 °C, solvent (1 mL).
[b] Determined by ^1H NMR spectroscopy, using 1,3,5-trimethoxybenzene as internal standard.



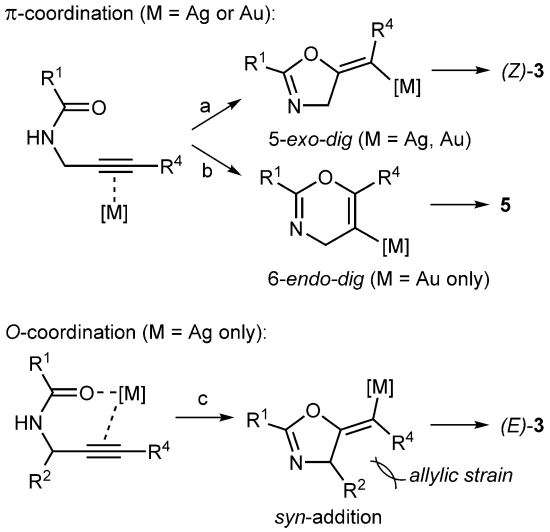
* Reactions were monitored by ^1H NMR in CD_2Cl_2. Products were not isolated due to volatility (**3b**, **3c**), low conversion (**3h**) or decomposition on silica gel (**3k**–**3m**).

Figure 1. *Reaction conditions:* Substrate **2a–p** (0.2 mmol), catalyst $[Ag(MeO\text{-}Py)_2]PF_6$ (1–15 mol%), CH_2Cl_2 (0.5 mL), 23 °C. Conversions determined by ^1H NMR spectroscopy (1,3,5-trimethoxybenzene as internal standard). Isolated yields after purification are indicated in parentheses.

stituted **2g**, even in refluxing DCE; presumably due to reduced *O*-nucleophilicity:

As expected, the presence of *gem*-dimethyl groups at the propargylic position afforded quantitative conversion to the product **3i** within an hour, using just 1 mol% of the catalyst. On the other hand, the introduction of an aromatic (PMP = *p*-methoxyphenyl) group at R^2 (**2j**) also afforded good yields of the **3j** in 30 min using 5 mol% of the catalyst. Encouraged by these results, the cyclization of the challenging non-terminal propargylic amides was examined, focussing initially on substrates where R^2 = PMP. We were delighted to find that substrates containing cyclopropyl, *n*-butyl, cyclohexenyl and phenyl cyclized smoothly to afford the corresponding 5-*exo-dig* products **3k**–**3p** in mostly good to excellent yields. The preservation of the cyclopropyl ring in **3k** is noteworthy, as it suggests that radical intermediates are unlikely to be involved in these reactions. Within this subset of substrates, mixtures of *E/Z*-isomers were obtained with alkyl substituents at R^4 (**3k**–**3m**), whereas only *Z*-isomer was obtained for phenyl-substituted substrates (**3n**–**3p**), irrespective of substitution at the propargylic position (R^2, R^3), i.e., the observed stereochemistry is likely to be (largely) associated with electronic, rather than steric, effects. In all cases, a long-range allylic (^4J) coupling of *ca.* 2.5 Hz for the alkenyl and methine protons is associated with the (*Z*)-configuration, confirmed by a NOESY experiment performed on **3m**, and an X-ray crystal structure obtained for **3n** (Supporting Information).

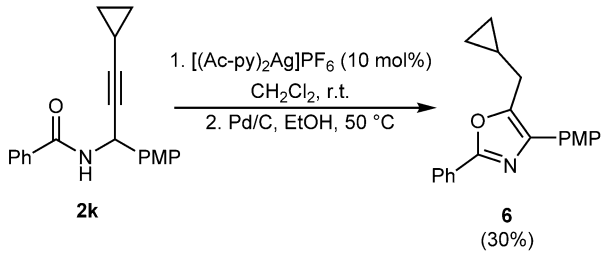
The different regio- and stereoselectivities exhibited by the silver- and gold-catalyzed reactions is particularly striking, and warrants further comment. For the (NHC)Au-catalyzed reactions, competitive formation of the oxazine product **5** was observed for substrates containing an alkyl substituent at R^4,[8] whereas the Ag catalyst only afforded the 5-membered heterocycle. Conversely, the Au-catalyzed reaction only afforded *Z*-**3**, whereas the *E*-isomer was obtained as a minor product using the Ag catalyst. Control experiments established that the *E/Z*-isomerization does not occur in the presence of triflic acid or the 4-methoxypyridinium hexafluorophosphate salt. Furthermore, the formation of *Z*- and *E*-**3** occurs simultaneously, their relative concentrations did not vary during the course of the reaction, suggesting that the two isomers are formed *via* competitive pathways. Three different reaction routes are proposed to account for these observations (Scheme 2). The principal mode of C≡C activation is by its coordination to the π-acidic metal centre, whereupon 5-*exo-dig* cyclization is generally favoured, to furnish a putative vinylmetallic intermediate that affords the *Z*-isomer after protodemetallation (pathway a). When R^4 = alkyl group, 6-*endo-dig* cyclization is favoured by a cationic Au-NHC catalyst (pathway b), which was attributed to electronic



Scheme 2. Rationalization of observed selectivities.

bias.[8a] In the presence of a basic pyridine, however, formation of the 5-membered heterocycle is favoured under silver catalysis. The formation of the *E*-isomer is explained by the greater Lewis acidity of the Ag catalyst than Au, so it could also coordinate to the amide functionality during the π-activation step, directing a *syn*-addition across the triple bond (pathway c). Such a simultaneous binding to alkyne and oxygen has been previously shown by DFT calculations to be energetically feasible in the Au-catalyzed reaction (although the formation of the *E*-isomer was not observed using gold catalysts).[8a] Under silver catalysis, this competitive pathway is prohibited when R^4 = Ph (as in compounds **3n** and **3o**), due to unfavourable allylic ($A^{1,3}$) interactions[9] between substituents R^2 and R^4. This is supported further by the increasing *Z/E* ratios obtained for products **3k–3m**.

Previous work by Hashmi and co-workers has shown that the *exo*-methylene group in oxazolines **3** may be oxidized using O_2,[10] halogenated using NXS,[11] or Alder-ene reactions,[12] to give added functionalities for further elaboration. As compounds **3k–3m** decomposed on silica gel, we attempted to telescope the cyclization process with other reactions that can lead to stable products. The aromatization of unsubstituted methylenic oxazolines (R^4 = H, including **3a**) has been reported to proceed in the presence of DBU at 50 °C.[13,14] During an attempt to reduce the C=C bond, however, we discovered that aromatization of **3k** also occurred in the presence of Pd/C, to give the compound **6** in low yield (Scheme 3); with further optimization, this may offer a possible alternative to the synthesis of trisubstituted oxazoles.[15]



Scheme 3. Synthesis of tri-substituted oxazole by a telescoped process.

Conclusions

Ag-catalyzed cyclization of propargylic amides occurs under mild conditions in the presence of electron-rich pyridyl ligands to afford 5-*exo*-*dig* oxazoline products exclusively. The different electronic demands observed between the ligand-accelerated N−H and O−H addition processes will require further investigations by DFT calculations. Under silver catalysts, the reaction is regioselective towards 5-*exo*-dig cyclization, producing a mixture of *E*- and *Z*-isomers with internal alkynes, whereby the product distribution is dependent on the pattern of substitution on the substrate. This is in contrast to the gold-catalyzed process, where the regioselectivity is less well-defined, yet produces only *Z*-isomers. Using this methdology, the synthesis of a trisubstituted oxazole (**6**) was demonstrated, including an alternative route to aromatize the products to their corresponding oxazoles over a heterogeneous Pd catalyst. This work has led us to explore other silver catalysts with enhanced reactivities, and these results will be reported in due course.

Experimental Section

General

All reactions involving silver compounds were performed in the dark by covering the reaction vessels with aluminium foil. Catalytic reactions were carried out in parallel in a Radley's 12-place reaction carousel, or in screw-cap vials. Solvents were dried by passage through the columns of molecular sieves in a solvent purification system (Innovative Technology Inc.). Unless otherwise stated, materials obtained from commercial suppliers were used without purification. Column chromatography was performed on silica gel (Kieselgel 60) or neutral alumina. Preparative TLC was performed on $20\times20\ cm^2$ glass plates with a 1.5 mm thick layer of silica gel 60 F_{254} (Analtech). TLCs were performed using silica gel 60 F_{254} aluminium sheets and visualized with $KMnO_4$ solution or exposure to UV light ($\lambda=254$ nm). ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded at 25 °C on Bruker Avance™ 400 spectrometers. Residual protic solvents were used as an internal standard and ^{13}C resonances were referenced to the deuterated carbon. Chemical shifts (δ) are reported in ppm. Multiplicity is abbreviated to s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), sept (septet), and multiplet (m). Melting points were recorded using an Electrothermal Gallenkamp apparatus, and are uncorrected. Mass spectra (MS) were recorded at Imperial College London on Micromass Autospec Premier, Micromass LCT Premier, or VG Platform II spectrometers using EI, CI or ESI techniques. Infrared spectra were recorded using a Perkin–Elmer 100 series FT-IR spectrometer, equipped with an ATR accessory. Single crystal X-ray diffraction was performed at Imperial College London using an Agilent Xcalibur 3 E diffractometer. Elemental analyses were performed by the Analytical Services at London Metropolitan University.

The syntheses and characterization data of silver complexes used in this work were described in our previous work.[1] Preparation procedures for acyclic precursors **2** are described in the Supporting Information. Characterization data for new compounds are given in the Supporting Information.

Representative Procedure for the Ag(I)-Catalyzed Conversion of 2 to 3

$[(MeO\text{-}Py)_2Ag]PF_6$ (1–15 mol%) was added to a solution of the propargylic amide substrate **2a** (2.0 mmol, 1 equiv.) in CH_2Cl_2 (5.0 mL) at room temperature. After the prescribed reaction time, the reaction mixture was filtered through Celite, and the filtrate concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/ethyl acetate). Copies of ^1H and ^{13}C NMR spectra are provided in the Supporting Information.

2-Phenyl-5-methylene-4,5-dihydrooxazole (3a):[2d] Purified by column chromatography (petroleum ether/ethyl acetate, 1:1); yield: 0.30 g (94%); yellow oil; ^1H NMR ($CDCl_3$): $\delta=$ 8.05–7.91 (m, 2H), 7.56–7.47 (m, 1H), 7.48–7.40 (m, 2H), 4.82 (q, $J=2.9$ Hz, 1H), 4.65 (t, $J=2.9$ Hz, 2H), 4.36 (q, $J=$ 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=163.7$, 158.8, 131.8, 128.5, 128.0, 126.7, 83.7, 57.7; HR-MS (ESI): $m/z=160.0751$, calcd. for $C_{10}H_9NO$ $[M+H]^+$: 160.0757; IR: $\nu_{max}=1692$ (C=C), 1647 cm^{-1} (C=N).

2-Methyl-5-methylene-4,5-dihydrooxazole (3b): The reaction was performed in CD_2Cl_2 and the product yield was calculated in the presence of a known amount of added internal standard (1,3,5-trimethoxybenzene). The product is too volatile to be isolated. ^1H NMR (CD_2Cl_2): $\delta=4.73$–4.71 (m, 1H), 4.47–4.44 (m, 2H), 4.34–4.33 (m, 1H), 2.12 (t, $J=$ 1.5 Hz, 3H).

2-*tert*-Butyl-5-methylene-4,5-dihydrooxazole (3c):[11] The reaction was performed in CD_2Cl_2 and the product yield was calculated in the presence of a known amount of added internal standard (1,3,5-trimethoxybenzene). The product is too volatile to be isolated. ^1H NMR (CD_2Cl_2): $\delta=4.52$ (dt, $J=3.0$, 2.4 Hz, 1H), 4.29 (t, $J=2.9$ Hz, 2H), 4.14 (dt, $J=3.0$, 2.4 Hz, 1H), 1.13 (s, 9H).

(*E*)-5-Methylene-2-styryl-4,5-dihydrooxazole (3d):[11] Purified by column chromatography (petroleum ether/ethyl acetate, 2:1); yield: 0.31 g (84%); white solid; ^1H NMR ($CDCl_3$): $\delta=7.60$–7.30 (m, 6H), 6.63 (d, $J=16.3$ Hz, 1H), 4.76 (q, $J=2.9$ Hz, 1H), 4.58 (t, $J=2.8$ Hz, 2H), 4.32 (q, $J=$ 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=163.5$, 158.5, 140.8, 134.9, 129.7, 128.9, 127.6, 114.1, 83.3, 57.7; HR-MS (ESI): *m/*

$z = 186.0916$, calcd. for $C_{12}H_{11}NO$ $[M+H]^+$: 186.0913; IR: $\nu_{max} = 1687$ (C=C), 1656 cm^{-1} (C=N).

Ethyl-(5-methylene-4,5-dihydro-1,3-oxazol-2-yl)acetate (3h):[11] This compound was not isolated due to the low yield of this compound (*ca.* 10% by NMR) and difficulties in separation from unreacted starting material. ^1H NMR ($CDCl_3$): $\delta = 4.70$ (q, $J = 3.0$ Hz, 1H), 4.46 (td, $J = 2.8$, 1.4 Hz, 2H), 4.30 (q, $J = 2.7$ Hz, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 3.43 (s, 2H), 1.28 (t, $J = 7.1$ Hz, 3H).

4,4-Dimethyl-5-methylene-2-phenyl-4,5-dihydrooxazole (3i):[2c] Purified by column chromatography (petroleum ether/ethyl acetate, 6:1); yield: 0.36 g (96%); colourless oil; ^1H NMR ($CDCl_3$): $\delta = 8.00$–7.98 (m, 2H), 7.54–7.47 (m, 1H), 7.47–7.40 (m, 2H), 4.74 (d, $J = 2.8$ Hz, 1H), 4.25 (d, $J = 2.9$ Hz, 1H), 1.45 (s, 6H); ^{13}C NMR ($CDCl_3$): $\delta = 167.9$, 159.8, 131.6, 128.4, 128.1, 127.0, 82.3, 69.1, 29.7; HR-MS (ESI): $m/z = 188.1074$, calcd. for $C_{12}H_{13}NO$ $[M+H]^+$: 188.1070; IR: $\nu_{max} = 1694$ (C=C), 1645 cm^{-1} (C=N).

4-(4-Methoxyphenyl)-5-methylene-2-phenyl-4,5-dihydro-1,3-oxazole (3j): Purified by column chromatography (petroleum ether/ethyl acetate, 4:1); yield: 0.48 g (90%); white solid; mp 75–81 °C; ^1H NMR ($CDCl_3$): $\delta = 8.10$–8.03 (m, 2H), 7.58–7.51 (m, 1H), 7.50–7.42 (m, 2H), 7.29–7.23 (m, 2H), 6.94–6.87 (m, 2H), 5.74 (t, $J = 2.8$ Hz, 1H), 4.91 (t, $J = 2.9$ Hz, 1H), 4.27 (t, $J = 2.7$ Hz, 1H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 162.7$, 162.6, 159.3, 132.7, 132.0, 128.5, 128.5, 128.3, 126.6, 114.2, 85.0, 71.8, 55.3; HR-MS (ESI): $m/z = 266.1174$, calcd. for $C_{17}H_{15}NO_2$ $[M+H]^+$: 266.1181; IR: $\nu_{max} = 1695$ (C=C), 1645 cm^{-1} (C=N); anal. calcd. for $C_{17}H_{15}NO_2$: C 76.96, H 5.70, N 5.28%; found: C 76.80, H 5.64, N, 5.20%.

(5*E*)-5-(Cyclopropylmethylene)-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole (*E*-3k): This compound decomposes on silica and was not isolated. ^1H NMR ($CDCl_3$): $\delta = 7.95$–7.93 (m, 2H), 7.43–7.36 (m, 3H), 7.29–7.27 (m, 2H), 6.90–6.88 (m, 2H), 5.19 (d, $J = 3.0$ Hz, 1H), 4.91 (d, $J = 3.0$ Hz, 1H), 3.79 (s, 3H), 1.58–1.51 (m, 1H), 0.90–0.86 (m, 2H), 0.78–0.72 (m, 2H).

(5*Z*)-5-(Cyclopropylmethylene)-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole (*Z*-3k): This compound decomposes on silica and was not isolated. ^1H NMR ($CDCl_3$): $\delta = 8.10$–8.08 (m, 2H), 7.55–7.51 (m, 1H), 7.47–7.43 (m, 2H), 7.24–7.22 (m, 2H), 6.90–6.87 (m, 2H), 5.70 (d, $J = 2.4$ Hz, 1H), 4.07 (dd, $J = 9.5$, 2.4 Hz, 1H), 3.79 (s, 3H), 1.85–1.76 (m, 1H), 0.84–0.73 (m, 2H), 0.42–0.32 (m, 2H).

(5*E*)-5-Pentylidene-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole (*E*-3l): This compound decomposes on silica and was not isolated. ^1H NMR ($CDCl_3$): $\delta = 8.01$–7.99 (m, 2H), 7.42–7.37 (m, 3H), 7.30–7.27 (m, 2H), 6.90–6.88 (m, 2H), 5.19 (d, $J = 2.8$ Hz, 1H), 4.84 (d, $J = 2.8$ Hz, 1H), 3.80 (s, 3H), 2.23 (t, $J = 7.5$ Hz, 2H), 1.63–1.56 (m, 2H), 1.50–1.43 (m, 2H), 0.95 (t, $J = 7.3$ Hz, 3H).

(5*Z*)-5-Pentylidene-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole (*Z*-3l): This compound decomposes on silica and was not isolated. ^1H NMR ($CDCl_3$): $\delta = 8.08$–8.06 (m, 2H), 7.47–7.44 (m, 3H), 7.25–7.23 (m, 2H), 6.90–6.88 (m, 2H), 5.68 (d, $J = 2.5$ Hz, 1H), 4.54 (td, $J = 7.5$, 2.5 Hz, 1H), 3.80 (s, 3H), 2.32–2.17 (m, 2H), 1.40–1.33 (m, 4H), 0.91 (t, $J = 7.1$ Hz, 3H).

(5*E*)-5-(1-Cyclohexenylmethylene)-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole (*E*-3m): This compound decomposes on silica and was not isolated. ^1H NMR ($CDCl_3$): $\delta = 8.07$–8.04 (m, 2H), 7.48–7.39 (m, 3H), 7.32–7.28 (m, 2H), 6.91–6.88 (m, 2H), 6.49 (t, $J = 4.0$ Hz, 1H), 5.27 (d, $J = 3.4$ Hz, 1H), 5.08 (d, $J = 3.4$ Hz, 1H), 3.80 (s, 3H), 2.27–2.21 (m, 2H), 2.20–2.12 (m, 2H), 1.75–1.62 (m, 4H).

(5*Z*)-5-(1-cyclohexenylmethylene)-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole (*Z*-3m): Purified by preparative TLC (petroleum ether/ethyl acetate, 4:1); yield: 0.34 g (49%); white solid; mp 116–120 °C; ^1H NMR ($CDCl_3$): $\delta = 8.09$–8.02 (m, 2H), 7.59–7.51 (m, 1H), 7.50–7.44 (m, 2H), 7.26–7.21 (m, 2H), 6.93–6.86 (m, 2H), 5.77 (br s, 1H), 5.71 (br s, 1H), 5.05 (br s, 1H), 3.80 (s, 2H), 2.54 (s, 2H), 2.12 (s, 2H), 1.78–1.67 (m, 2H), 1.64–1.56 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 162.7$, 159.3, 152.4, 133.3, 133.2, 131.9, 128.5, 128.3, 126.9, 126.8, 114.2, 106.1, 73.2, 55.3, 27.8, 25.9, 23.0, 22.0; HR-MS (ESI): $m/z = 346.1807$, calcd. for $C_{23}H_{23}NO_2$ $[M+H]^+$: 346.1818; IR: $\nu_{max} = 1686$ (C=C), 1646 cm^{-1} (C=N). anal. calcd. for $C_{23}H_{23}NO_2$: C 79.97, H 6.71, N 4.05%; found: C 79.92, H, 6.64, N 4.03%.

(5*Z*)-5-Benzylidene-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole (*Z*-3n): Purified by column chromatography (petroleum ether/ethyl acetate, 4:1); yield: 0.56 g (82%); white solid. X-ray diffraction quality single crystals were grown from CH_2Cl_2/hexane at −20 °C; mp 160–163 °C; ^1H NMR ($CDCl_3$): $\delta = 8.17$–8.15 (m, 2H), 7.62–7.54 (m, 3H), 7.54–7.52 (m, 2H), 7.40–7.38 (m, 2H), 7.31–7.28 (m, 2H), 6.94–6.90 (m, 1H), 6.94–6.90 (m, 2H), 5.93 (d, $J = 2.4$ Hz, 1H), 5.52 (d, $J = 2.4$ Hz, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 162.6$, 159.5, 155.7, 134.8, 132.5, 132.2, 128.9, 128.6, 128.5, 128.4, 128.0, 127.0, 126.4, 114.3, 102.8, 73.7, 55.3; HR-MS (ESI): $m/z = 342.1500$, calcd. for $C_{23}H_{19}NO_2$ $[M+H]^+$: 342.1494; IR: $\nu_{max} = 1692$ (C=C), 1650 cm^{-1} (C=N); anal. calcd. for $C_{23}H_{19}NO_2$: C 80.92, H 5.61, N 4.10%; found: C 81.13, H 5.56, N 4.05%. Crystal data for (*Z*)-**3n** have been deposited at the Cambridge Crystallographic Database, reference code: CCDC 1053097. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

(5*Z*)-5-Benzylidene-2-phenyl-4,5-dihydro-1,3-oxazole (*Z*-3o):[8b] Purified by column chromatography (petroleum ether/ethyl acetate, 6:1); yield: 0.19 g (40%); white solid; ^1H NMR ($CDCl_3$): $\delta = 8.11$–8.02 (m, 4H), 7.66–7.16 (m, 6H), 5.66 (t, $J = 2.6$ Hz, 1H), 4.81 (d, $J = 2.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 164.1$, 151.8, 134.9, 132.2, 130.8, 128.8, 128.7, 128.3, 128.0, 126.4, 100.9, 59.5; HR-MS (ESI): m/z = 236.1076, calcd. for $C_{16}H_{14}NO$ $[M+H]^+$: 236.1075.

(*Z*)-5-Benzylidene-4,4-dimethyl-2-phenyl-4,5-dihydrooxazole (*Z*-3p):[16] Purified by column chromatography (petroleum ether/ethyl acetate, 6:1); yield: 0.48 g (92%); white solid; ^1H NMR ($CDCl_3$): $\delta = 8.11$M–8.09 (m, 2H), 7.66–7.65 (m, 2H), 7.58–7.48 (m, 3H), 7.40 (t, $J = 7.8$ Hz, 2H), 7.24–7.21 (m, 1H), 5.55 (s, 1H), 1.54 (s, 6H); ^{13}C NMR ($CDCl_3$): $\delta = 160.7$, 159.9, 135.0, 131.9, 128.6, 128.5, 128.3, 127.9, 126.9, 126.2, 99.4, 70.9, 29.7. HR-MS (ESI): $m/z = 264.1396$, calcd. for $C_{18}H_{18}NO$ $[M+H]^+$: 264.1388.

Procedure for the Synthesis of 6 (Unoptimized)

$[(Ac\text{-}Py)_2Ag]PF_6$ (0.1 mmol, 47.1 mg, 0.1 equiv.) was added to a solution of the substrate **2k** (1.0 mmol, 0.31 g, 1.0 equiv,) in CH_2Cl_2 (2.5 mL) in a 10-mL round-bottomed

flask. The reaction mixture was stirred at room temperature for 12 h, before it was filtered through basic alumina and evaporated under vacuum. Absolute ethanol (4 mL) and Pd/C (10 mol% Pd) were then added to the residue and the resulting mixture was heated at 50 °C for 2 h. After cooling, the solvent was evaporated and the resulting oily residue purified by column chromatography on silica (petroleum ether:ethyl acetate, 6:1) to afford the oxazole product as a white solid; yield: 91.6 mg (30%). ^{1}H NMR ($CDCl_3$): δ = 8.10–8.08 (m, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.46–7.44 (m, 3H), 6.98 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.87 (d, J = 6.6 Hz, 2H), 1.19–1.12 (m, 1H), 0.58–0.55 (m, 2H), 0.32–0.30 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 159.0, 146.5, 135.8, 129.9, 129.2, 128.6, 128.3, 127.8, 126.2, 125.0, 114.0, 55.3, 30.3, 9.8, 4.4; HR-MS (ESI): m/z = 306.1375, calcd. for $C_{20}H_{20}NO_2$ $[M+H]^+$: 306.1494.

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