CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.201200046

Gold Catalysis: One-Pot Alkylideneoxazoline Synthesis/Alder-Ene Reaction

A. Stephen K. Hashmi* and Anna Littmann[a]

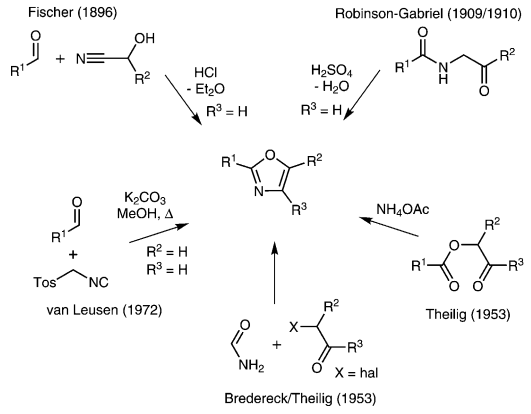
Abstract: Based on the gold-catalyzed synthesis of methyleneoxazolines, a one-pot combination with an Alder-ene reaction was developed. For azodicarboxylates, good to very good yields (51–99%) of the oxazolemethylhydrazinedicarboxylates were achieved with 3 mol% of the Gagosz catalyst, [$Ph_3PAuNTf_3$]. In a less-selective reaction, 4-phenyl-3H-1,2,4-triazol-3,5(4H)-dione gave lower yields (41–49%) of the corresponding oxazolemethylphenyltriazolidinediones. Overall, five new bonds were formed. Tetracyanoethylene afforded a cyclobutane derivative through a [2+2] cycloaddition reaction at −40 °C, but only 45% of the spiro compound was obtained. The less-readily available KITPHOS ligands on gold gave even higher yields at lower catalyst loadings (2 mol%), but longer reaction times were required.

Keywords: alkynes · amides · gold · heterocycles · oxazoles

Introduction

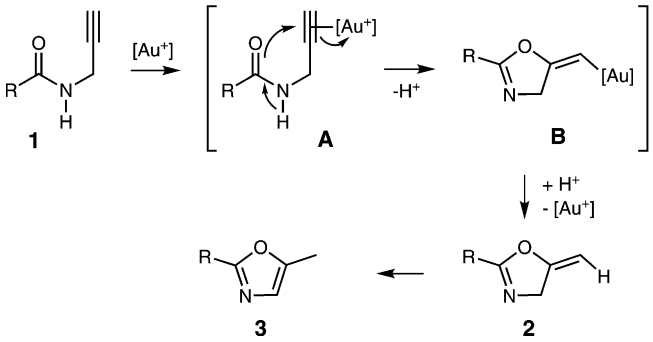
The oxazole ring,[1] 5-methyloxazoles,[2] and functionalized 5-methyloxazoles[3] are prevalent in many natural products and pharmaceutically active compounds. Thus, an efficient synthesis of such compounds is very important.

One of the classical routes to synthesize oxazoles is the Robinson–Gabriel synthesis (Scheme 1)[4a–c] by using acylated aminoketones and dehydrating reagents, such as PCl_5, $SOCl_2$, or even concentrated sulfuric acid. Other routes include the Fischer oxazole synthesis,[4d] the methods developed by Theilig[5] and by Bredereck and co-workers,[4e,f] and the van Leusen oxazole synthesis.[4g,h] *N*-Propargylcarboxamides have long been recognized as precursors to oxazoles, and initially sulfuric acid or mercury(II) acetate were used for their conversion.[6] In 1989, Hacksell and co-workers discovered a conversion that was catalyzed by strong bases.[7] *N*-Propargylimidates were also reported to be suitable starting materials,[8] although neither of these methods had good functional-group tolerance.



Scheme 1. Different known routes to oxazole heterocycles.

The first transition metal-catalyzed oxazole syntheses with high functional-group tolerance were published by Cacchi and co-workers in 2001[9] and by Costa and co-workers in 2002,[10] both of them used palladium catalysis. Several subsequent syntheses were reported by Müller and co-workers, among others.[11] In 2004, we reported the conversion of *N*-propargylcarboxamides (**1**) into 5-methyloxazoles (**3**) by using 2 mol% gold(III) chloride (Scheme 2);[12] this method has since been applied in academic[13] and industrial research.[14] Alkylideneoxazolines (**2**) were determined to be intermediates in the reaction, and an initial *anti*-oxyauration step was observed after the coordination of the triple bond to the gold catalyst (Scheme 2).[12] At the same time,



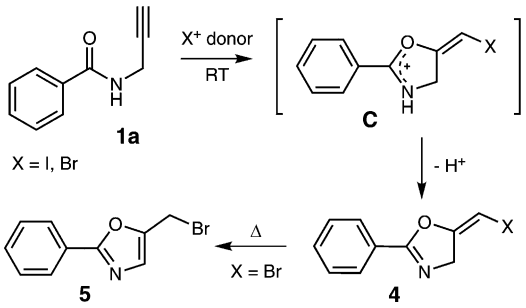
Scheme 2. Mechanism of the gold-catalyzed conversion of compound **1** into compound **3**.

[a] Prof. Dr. A. S. K. Hashmi, Dipl.-Chem. A. Littmann
Organisch-Chemisches Institut
Ruprecht-Karls-Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
Fax: (+49) 6221-54-4205
E-mail: hashmi@hashmi.de

Uemura and co-workers also published a gold-catalyzed synthesis of oxazoles[15] from a one-pot reaction that included the ruthenium-catalyzed formation of the *N*-propargylcarboxamides from carboxamides and propargylic alcohols; however, 20 mol% of gold(III) chloride was required in this process. In 2006, we showed that the use of gold(I) catalysts stopped the reaction at the alkylideneoxazoline stage;[16] this result has also found broad application in the screening of new catalysts.[17]

Although the conditions for the gold-catalyzed pathway are intrinsically mild, and neither oxygen nor humidity need to be excluded,[18] there is still a major drawback: all of the oxazoles that were formed as the final products contained simple methyl groups; in the presence of more-complex substituents, oxazines were preferentially formed instead.[17e,19] However, the rapid and easy access to compounds **2** by gold(I) catalysis made the use of these versatile building blocks more feasible. Hence, their functionalization should be possible.

In 1981, Caristi and co-workers reported the preparation of halomethyloxazolines (Scheme 3), which are potential synthetic intermediates in the synthesis of functionalized oxazoles.[20] The reaction of compound **1a** with a Br^+ or I^+ donor gave halomethyloxazoline **4**. Heating compound **4** afforded compound **5** when X = Br, whereas the reaction with the iodo-derivative of compound **4** failed.



Scheme 3. The direct halogenation reaction as a route to functionalized oxazoles was unselective.

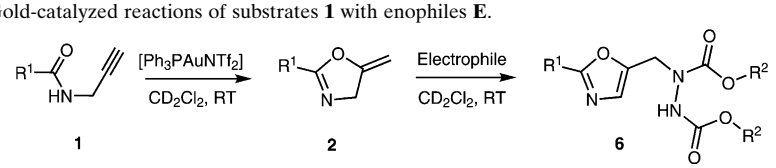
The reaction of compound **1a** with *N*-bromosuccinimide also gave compound **5**.[21] Whilst these halogen derivatives are potential candidates for the preparation of methyl-functionalized derivatives of compound **3**, their synthesis is still troublesome and they are very sensitive, even if prepared by combining gold catalysts and halogenation reagents.[22,23]

Herein, we report the first reactions of alkylideneoxazolines **2** with nitrogen electrophiles in Alder-ene reactions.

Results and Discussion

Substrates **1b**–**1f**, which contained R = *t*Bu, Bn, thienyl, cyclopropyl, and adamantly substituents, respectively, were prepared according to literature procedures.[12,16,23] First, we tested the stepwise addition of the substrates in a one-pot procedure (Table 1, method A): substrate **1** and gold catalyst [$Ph_3PAuNTf_2$] (Gagosz's catalyst)[24] were mixed together. After reaction time t_1, complete conversion into compound **2** was detected by ^1H NMR spectroscopy. Then, the enophile (**E**, an azodicarboxylate) was added and, after reaction time t_2, the conversion was complete and the product was isolated. All of the conversion reactions were conducted under mild conditions at room temperature. The reaction times strongly depended on the substrate and on the enophile. For both steps, that is, the gold-catalyzed cycloisomerization and Alder-ene reactions, the rates of reaction varied significantly and there was no clear trend in terms of substrate **1**. Compound **1b** (Table 1, entries 1–3) reacted faster than compound **1d** (Table 1, entries 8–10), whilst compound **1c** was the slowest of the substrates tested (Table 1, entries 4–7). We could not detect any influence of the gold catalyst on the Alder-ene reaction; from the observed rates of reaction, there was no evidence for a participation of gold as a catalyst in the pericyclic reaction. For enophiles (**E**) with increasing steric bulk, longer reaction times were observed for the reactions with compounds **1b** (Table 1, entries 1–3) and **1c** (Table 1, entries 4–7); for the planar-thienyl-substituted substrate (**1d**), quite similar reaction times were detected. However, apart from these details, the yields were good to excel-

Table 1. Gold-catalyzed reactions of substrates **1** with enophiles **E**.



Entry	**1** (R^1)	**E** (R^2)	t_1[a]	t_2[b]	Yield (method A) [%]	t_3[c]	Yield (method B) [%]	Product
1	**1b** (*t*Bu)	**Ea** (Et)	0.5 h	1.5 h	91	4 h	89	**6a**
2	**1b** (*t*Bu)	**Eb** (*i*Pr)	0.5 h	7 h	96	1 d	95	**6b**
3	**1b** (*t*Bu)	**Ec** (*t*Bu)	0.5 h	3 d	87	3 d	81	**6c**
4	**1c** (Bn)	**Ea** (Et)	14 h	5 h	66	14 h	81	**6d**
5	**1c** (Bn)	**Eb** (*i*Pr)	14 h	27 h	88	2 d	92	**6e**
6	**1c** (Bn)	**Ec** (*t*Bu)	14 h	3 d	96	3 d	86	**6f**
7	**1c** (Bn)	**Ed** (Bn)	14 h	16 h	51	20 h	88	**6g**
8	**1d** (thienyl)	**Ea** (Et)	1 h	2 h	98	3 h	96	**6h**
9	**1d** (thienyl)	**Eb** (*i*Pr)	1 h	10 h	95	13 h	99	**6i**
10	**1d** (thienyl)	**Ec** (*t*Bu)	1 h	1 d	98	40 h	86	**6j**
11	**1e** (cyclopropyl)	**Ea** (Et)	10 h	2 d	53	3 d	66	**6k**
12	**1f** (adamantyl)	**Ec** (*t*Bu)	–	–	–	45 h	85	**6l**

[a] Reaction time after addition of the catalyst; [b] reaction time after addition of the enophile; [c] reaction time according to method B.

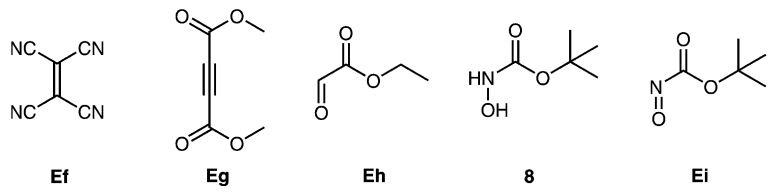
lent, the only exception being cyclopropyl derivative **1e** (Table 1, entry 11), which did not react selectively, and instead formed unidentified oligomeric side-products.

Next, we conducted the same reactions by mixing compounds **1**, enophiles **E**, and the catalyst altogether (Table 1, method B). Experiments with only the substrate and enophile showed that there was no direct reaction between these two components; the Alder-ene reaction was not observed until after the cycloisomerization reaction to afford compound **2**. We were delighted to see that the enophiles (**E**) did not inhibit the gold catalysts, which once more demonstrated a weak Au^I–N interaction.[25] However, the overall reaction time (t_3) was clearly slower (compared to t_1+t_2); thus, the presence of the enophile slightly inhibited the catalysis. With regard to the yield, in most cases, the results of the step-wise addition from method A could almost be matched (Table 1, entries 1–3, 6, 8, and 10). In five cases, slightly higher yields were obtained (Table 1, entries 4, 5, 7, 9, and 11). This result was due, in part, to the more-sensitive intermediate (**2**) being exposed to the enophile immediately, which reduced the opportunity for competing side-reactions to occur. For Table 1, entries 7, 9, and 11, the longer overall reaction times might also contribute to the higher yield. For compounds **1f** and **Ec**, only method B was used, and a very good yield (85%) was obtained (Table 1, entry 12).

Next, we tested amides **1b**–**1d** with [$Ph_3PAuNTf_2$] and the very reactive dienophile 4-phenyl-3H-1,2,4-triazol-3,5(4H)-dione (**Ee**; Table 2).

Unlike the reactions with azodicarboxylates **Ea**–**Ed**, the reactions with enophile **Ee** afforded only moderate yields. The very high reactivity of enophile **Ee** led to a loss of selectivity, owing to competing side-reactions and subsequent reactions of **Ee**, as indicated by a large number of TLC spots at higher polarity. Because compounds **7** are less interesting from a synthetic point of view than compounds **6**,[26] we did not investigate this point in detail.

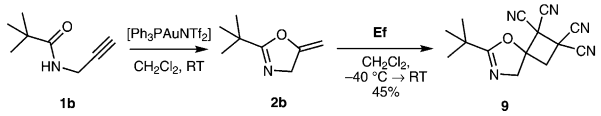
Further experiments to prepare substituted oxazoles by using Alder-ene reactions were performed with compound **1b** and tetracyanoethylene (**Ef**), as well as with compound **1c** and electrophiles **Eg**–**Ei** (Scheme 4).



Scheme 4. Other enophiles tested.

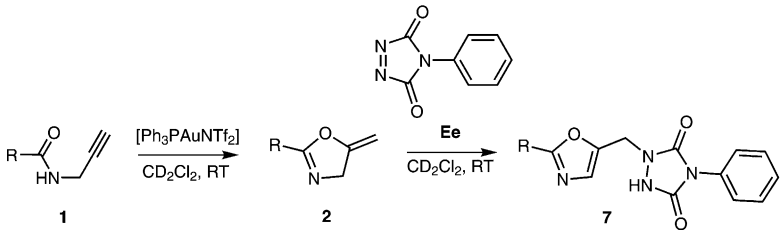
The addition of enophile **Ef** to intermediate **2b**, which had previously been generated from the cyclization of compound **1b**, was conducted at −40 °C. If the addition was done at room temperature, a fast and unselective decomposition of the reaction mixture was observed, and a black tar was formed. For the reaction with enophile **Ei**, 1 equivalent of tetrabutylammonium periodate was added to in situ oxidize compound **8** into enophile *tert*-butylnitrosoformate (**Ei**; Scheme 4).

The only successful conversion was the reaction with enophile **Ef**, in which a moderate yield of spiro compound **9** was obtained (Scheme 5). A [2+2]-cycloaddition pathway with the enol ether-like substructure of compound **2b**



Scheme 5. The formation of a four-membered ring was observed with enophile **Ef**.

Table 2. Yields and reaction times for the gold-catalyzed reactions of compounds **1a**–**1c** and enophile **Ee** to afford compounds **7a**–**7c**.



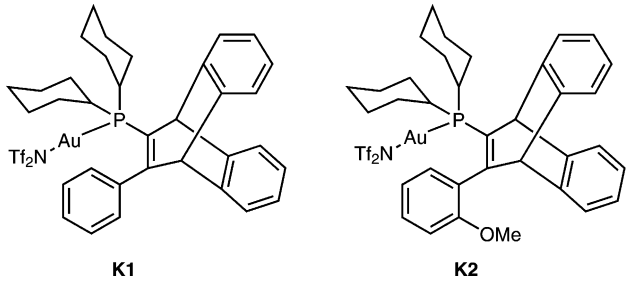
Entry	**1** (R^1)	t_1[a]	t_2[b]	Yield (method A) [%]	t_3[c]	Yield (method B) [%]	Product
1	**1b** (*t*Bu)	0.5 h	1.5 h	89	3 d	46	**7a**
2	**1c** (Bn)	14 h	1.5 h	22	4 d	41	**7b**
3	**1d** (thienyl)	1 h	2 h	41	11 d	49	**7c**

[a] Reaction time after addition of the catalyst; [b] reaction time after addition of the enophile; [c] reaction time according to method B.

seemed to be preferred with this reagent. Once more, the reaction was unselective, thereby providing several unidentified polar side-products.

Even after heating at 100 °C for 2 hours, the reaction between compound **1c** and enophile **Eg** did not show any conversion into product **2b** in the ^{1}H NMR spectrum. On the other hand, in the reaction of compound **1c** with either enophile **Eh** or **Ei**, complete consumption of compound **2c** was observed. However, only complex mixtures of products were formed, and no defined product could be isolated and characterized.

To compare the catalytic efficiency of [$Ph_3PAuNTf_2$] with that of other catalysts, we used compound **1c** and enophile **Ec** in the reaction with gold(I) complexes **K1** and **K2** (Scheme 6). These



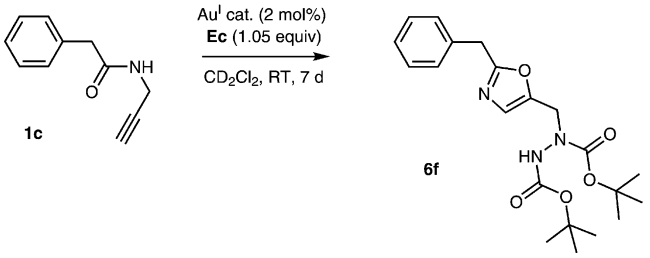
K1 K2

Scheme 6. Catalysts **K1** and **K2**, which contained ligands from the KITPHOS family.

catalysts had been used in the synthesis of alkylideneoxazolines with great success.[16a–c]

All reactions were performed in an NMR tube. Compound **1c** and enophile **Ec** were dissolved in CD_2Cl_2; then, 2 mol% of catalyst [$Ph_3PAuNTf_2$], **K1**, or **K2** was added. The reactions in the presence of catalysts **K1** and **K2** were slower than with [$Ph_3PAuNTf_2$], although they were more long-living with regards to their activity. After 7 days, no further conversion was detectable by ^{1}H NMR spectroscopy. The yields were determined by using 1,3,5-tri-*tert*-butylbenzene as an internal standard (Table 3).

Table 3. A comparison of different gold catalysts.



Entry	Catalyst	Yield of **6f** [%]
1	[$Ph_3PAuNTf_2$]	84
2	**K1**	92
3	**K2**	98

A loading of 2 mol% of [$Ph_3PAuNTf_2$] gave a lower yield of the product than with 3 mol% (84% versus 86%; Table 1, entries 1 and 6). Catalyst **K1** gave a higher yield (Table 3, entry 2), but the best catalyst was **K2**. However, because the differences were not significant, and because catalyst **K1** is commercially available whilst **K2** had to be prepared, for most applications, catalyst **K1** is probably the more-convenient catalyst.

Conclusions

The combination of the gold-catalyzed alkylidene–oxazoline synthesis and the Alder-ene reaction allowed the synthesis of functionalized oxazoles in a two-component, one-pot reaction. Neither the enophile nor the hydrazine-type products, both of which were potential ligands, significantly inhibited the catalyst. With highly reactive enophiles, complete selectivity was not achieved, with the formation of some side-products, such as [2+2]-cycloaddition products. With weak dienophiles, no reaction was observed.

This first successful organic transformation of alkylidene–oxazolines into functionalized oxazoles will form the basis for a detailed study of the use of other synthetically important enophile building blocks, including in the analogous asymmetric reactions.

Experimental Section

General Procedure for the Cyclization of Propargylamides into Methylenedihydrooxazoles, Followed by the Addition of Electrophiles

Method A: In an NMR tube, a solution of propargylcarboxamide in CD_2Cl_2 (600 μL) was treated with [$Ph_3PAuNTf_2$]. When the cyclization was complete (t_1), as monitored by ^{1}H NMR spectroscopy, the enophile was added. The progress of the second step was also monitored by ^{1}H NMR spectroscopy, and, when the reaction was complete (t_2), the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel.

Method B: In an NMR tube, the catalyst [$Ph_3PAuNTf_2$] was added to a solution of the propargylcarboxamide and the electrophile in CD_2Cl_2 (600 μL). After the reaction was complete (t_3), as monitored by ^{1}H NMR spectroscopy, the solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel.

*Diethyl-1-((2-tert-butyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6a**)*

Diethyl-1-((2-*tert*-butyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to methods A (t_1 = 30 min, t_2 = 1.5 h) and B (t_3 = 4 h). In method A, compound **1b** (27.0 mg, 194 μmol), enophile **Ea** (33.8 mg, 194 μmol), and [$Ph_3PAuNTf_2$] (3.41 mg, 4.61 μmol) were used. In method B, compound **1b** (15.0 mg, 108 μmol), enophile **Ea** (19.0 mg, 109 μmol), and [$Ph_3PAuNTf_2$] (2.37 mg, 3.21 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 2:1) afforded compound **6a** (method A: 55.0 mg, 176 μmol, 91%; method B: 30.0 mg, 95.7 μmol, 89%) as a colorless oil.

R_f (petroleum ether/EtOAc, 2:1): 0.15; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 1.12–1.18 (m, 6H), 1.25 (s, 9H), 4.03–4.14 (m, 4H), 4.57 (s, 2H), 6.73 (s, 1H), 6.80 ppm (brs, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 14.4 (q), 14.7 (q), 28.6 (q, 3C), 34.0 (s), 45.0 (t), 62.4 (t), 63.2 (t), 125.7 (d), 146.8 (s), 156.2 (s), 171.1 (s), 171.2 ppm (s); IR (film): $\tilde{\nu}$ = 3293, 2977, 2935, 1720, 1555, 1515, 1467, 1414, 1383, 1336, 1266, 1201, 1148, 1115, 1096, 1061, 1029, 992, 762, 670 cm^{-1}; MS (ESI): *m/z* (%): 627 (35) [M_2+H]$^+$, 314 (100) [*M*+H]$^+$, 110 (4), 101 (6), 96 (5), 89 (5); HRMS (ESI): *m/z* calcd for [$C_{14}H_{24}N_3O_5$]$^+$: 314.1711; found: 314.1709; elemental analysis calcd (%) for $C_{14}H_{23}N_3O_5$: C 53.66, H 7.40, N 13.41; found: C 53.32, H 7.44, N 13.04.

*Diisopropyl-1-((2-tert-butyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6b**)*

Diisopropyl-1-((2-*tert*-butyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to methods A (t_1 = 0.5 h, t_2 = 7 h) and B (t_3 = 1 d). In method A, compound **1b** (33.5 mg, 241 μmol), enophile **Eb** (68.2 mg, 337 μmol), and [$Ph_3PAuNTf_2$] (4.91 mg, 6.64 μmol) were used. In method B, compound **1b** (22.4 mg, 161 μmol), enophile **Eb** (44.5 mg, 220 μmol), and [$Ph_3PAuNTf_2$] (3.58 mg, 4.84 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 3:1) afforded compound **6b** (method A: 79.0 mg, 231 μmol, 96%; method B: 52.0 mg, 152 μmol, 95%) as a colorless oil.

R_f (petroleum ether/EtOAc, 2:1): 0.27; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 1.19–1.29 (m, 12H), 1.32 (s, 9H), 4.62 (s, 2H), 4.82–4.99 (m, 2H), 6.53–6.71 (brs, 1H), 6.79 ppm (s, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 22.1 (q, 2C), 22.2 (q, 2C), 28.7 (q, 3C), 34.0 (s), 43.8 (t), 70.2 (d), 71.0 (d),

125.6 (d), 147.0 (s), 155.7 (s), 171.7 ppm (s, 2C); IR (film): $\tilde{\nu}$=3300, 2196, 1715, 1555, 1468, 1410, 1386, 1375, 1263, 1227, 1206, 1181, 1146, 1108, 1036, 996, 956, 864, 797, 713, 679 cm^{-1}; MS (ESI): *m/z* (%): 705 (100), 683 (13) $[M_2+H]^+$, 342 (93) $[M+H]^+$, 108 (6), 101 (8), 89 (4); HRMS (ESI): *m/z* calcd for $[C_{16}H_{28}N_3O_5]^+$: 342.2024 $[M+H]^+$; found: 342.2024.

*Di-tert-butyl-1-((2-tert-butyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6c**)*

Di-*tert*-butyl-1-((2-*tert*-butyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to methods A (t_1=0.5 h, t_2=3 d) and B (t_3=3 d). In method A, compound **1b** (30.6 mg, 220 μmol), enophile **Ec** (51.5 mg, 224 μmol), and $[Ph_3PAuNTf_2]$ (4.76 mg, 6.44 μmol) were used. In method B, compound **1b** (20.1 mg, 144 μmol), enophile **Ec** (35.6 mg, 155 μmol), and $[Ph_3PAuNTf_2]$ (3.56 mg, 4.82 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 2:1) afforded compound **6c** (method A: 71.0 mg, 192 μmol, 87%; method B: 43.0 mg, 116 μmol, 81%) as a colorless oil.

R_f (petroleum ether/EtOAc, 2:1): 0.12; ^{1}H NMR (300 MHz, CD_2Cl_2): δ= 1.31 (s, 9H), 1.42 (s, 9H), 1.44 (s, 9H), 4.57 (s, 2H), 6.76 (s, 1H), 6.92–7.06 ppm (brs, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=28.3 (q, 3C), 28.3 (q, 3C), 28.7 (q, 3C), 34.0 (s), 45.6 (t), 81.3 (s), 81.9 (s), 125.3 (d), 147.4 (s), 155.2 (s), 171.5 ppm (s, 2C); IR (film): $\tilde{\nu}$=3122, 2974, 2934, 2361, 2305, 2196, 1775, 1715, 1555, 1503, 1475, 1424, 1365, 1270, 1224, 1145, 993, 955, 771, 744, 712, 694, 677 cm^{-1}; MS (EI(+), 70 eV): *m/z* (%): 369 (2) $[M]^+$, 293 (3), 281 (3), 269 (42), 257 (17), 253 (5), 242 (5), 241 (9), 240 (70), 213 (49), 212 (16), 197 (34), 196 (11), 170 (8), 169 (81), 168 (9), 156 (5), 153 (89), 152 (26), 140 (14), 139 (100), 121 (14), 118 (6); HRMS (EI(+), 70 eV): *m/z* calcd for $[C_{18}H_{31}N_3O_5]^+$: 369.2264; found: 369.2300.

*Diethyl-1-((2-benzyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6d**)*

Diethyl-1-((2-benzyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to methods A (t_1=14 h, t_2=5 h) and B (t_3=14 h). In method A, compound **1c** (19.0 mg, 110 μmol), enophile **Ea** (21.0 mg, 110 μmol), and $[Ph_3PAuNTf_2]$ (2.43 mg, 3.29 μmol) were used. In method B, compound **1c** (12.9 mg, 74.5 μmol), enophile **Ea** (17.0 mg, 97.6 μmol), and $[Ph_3PAuNTf_2]$ (1.84 mg, 2.49 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 1:1) afforded compound **6d** (method A: 25.0 mg, 72.0 μmol, 66%; method B: 21.0 mg, 60.5 μmol, 81%) as a colorless oil.

R_f (petroleum ether/EtOAc, 4:1): 0.14; ^{1}H NMR (300 MHz, CD_2Cl_2): δ= 1.17–1.26 (m, 6H), 4.05 (s, 2H), 4.08–4.20 (m, 4H), 4.64 (s, 2H), 6.73–6.80 (brs, 1H), 6.86 (s, 1H), 7.21–7.31 ppm (m, 5H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=14.5 (q), 14.5 (q), 34.8 (t), 45.1 (t), 62.4 (t), 63.2 (t), 126.3 (d), 127.3 (d), 128.9 (d, 2C), 129.1 (d, 2C), 136.0 (s), 147.6 (s, 2C), 156.5 (s), 163.6 ppm (s); IR (film): $\tilde{\nu}$=3283, 2983, 2933, 1717, 1561, 1497, 1468, 1455, 1426, 1383, 1263, 1227, 1197, 1111, 1061, 1028, 996, 764, 729, 697 cm^{-1}; MS (EI(+), 70 eV): *m/z* (%): 347(3) $[M]^+$, 260 (19), 259 (100), 258 (74), 214 (17), 187 (19), 186 (11), 173 (79), 172 (100), 171 (24), 167 (68), 144 (20), 117 (27), 103 (11), 91 (88); HRMS (EI(+), 70 eV): *m/z* calcd for $[C_{17}H_{21}N_3O_5]^+$: 347.1481; found: 347.1436.

*Diisopropyl-1-((2-benzyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6e**)*

Diisopropyl-1-((2-benzyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to methods A (t_1=14 h, t_2=27 h) and B (t_3=2 d). In method A, compound **1c** (21.0 mg, 121 μmol), enophile **Eb** (27.8 mg, 137 μmol), and $[Ph_3PAuNTf_2]$ (2.62 mg, 3.54 μmol) were used. In method B, compound **1c** (30.6 mg, 177 μmol), enophile **Eb** (49.5 mg, 245 μmol), and $[Ph_3PAuNTf_2]$ (3.70 mg, 5.00 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 2:1) afforded compound **6e** (method A: 40.0 mg, 107 μmol, 88%; method B: 61.0 mg, 162 μmol, 92%) as a colorless oil.

R_f (petroleum ether/EtOAc, 1:1): 0.25; ^{1}H NMR (300 MHz, CD_2Cl_2): δ= 1.22 (d, ^2J=6.9 Hz, 12H), 4.05 (s, 2H), 4.62 (s, 2H), 4.82–5.00 (m, 2H), 6.61–6.79 (brs, 1H), 6.85 (s, 1H), 7.22–7.34 ppm (m, 5H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=22.1 (q, 2C), 22.2 (q, 2C), 34.9 (t), 44.7 (t), 70.2 (d), 71.0 (d), 126.2 (d), 127.4 (d), 129.0 (d, 2C), 129.2 (d, 2C), 136.1 (s), 147.9 (s, 2C), 155.8 (s), 163.6 ppm (s); IR (film): $\tilde{\nu}$=3302, 2982, 2937, 1718, 1562, 1497, 1468, 1455, 1409, 1386, 1376, 1265, 1198, 1181, 1145, 1108, 1038, 998, 165, 728, 697 cm^{-1}; MS (EI(+), 70 eV): *m/z* (%): 375 (2) $[M]^+$, 316(5), 274 (15), 273 (69), 272 (57), 246 (7), 231 (27), 230 (7), 229 (7), 214 (44), 187 (45), 186 (16), 181 (16), 174 (11), 173 (90), 172 (100), 117 (13), 91 (44); HRMS (EI(+), 70 eV): *m/z* calcd for $[C_{19}H_{25}N_3O_5]^+$: 375.1794; found: 375.1779; elemental analysis calcd (%) for $C_{19}H_{25}N_3O_5$: C 60.79, H 6.71, N 11.19; found: C 60.44, H 6.81, N 10.76.

*Di-tert-butyl-1-((2-benzyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6f**)*

Di-*tert*-butyl-1-((2-benzyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to methods A (t_1=14 h, t_2=3 d) and B (t_3=3 d). In method A, compound **1c** (29.0 mg, 167 μmol), enophile **Ec** (41.2 mg, 179 μmol), and $[Ph_3PAuNTf_2]$ (3.71 mg, 5.02 μmol) were used. In method B, compound **1c** (40.0 mg, 231 μmol), enophile **Ec** (55.7 mg, 242 μmol), and $[Ph_3PAuNTf_2]$ (5.18 mg, 7.00 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 3:1) afforded compound **6f** (method A: 59.0 mg, 160 μmol, 96%; method B: 80.0 mg, 198 μmol, 86%) as a pale yellow oil.

R_f (petroleum ether/EtOAc, 2:1): 0.30; ^{1}H NMR (300 MHz, CD_2Cl_2): δ= 1.44 (s, 18H), 4.05 (s, 2H), 4.57 (s, 2H), 6.59 (s, 1H), 6.85 (s, 1H), 7.22–7.34 ppm (m, 5H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=28.3 (q, 6C), 34.6 (t), 43.9 (t), 81.5 (s), 82.1 (s), 126.0 (d), 127.3 (d), 129.0 (d, 2C), 129.2 (d, 2C), 136.1 (s), 148.3 (s), 155.2 (s), 163.5 ppm (s); IR (film): $\tilde{\nu}$=3307, 2979, 2932, 2305, 1715, 1562, 1496, 1479, 1455, 1393, 1368, 1278, 1255, 1154, 1110, 998, 956, 856, 759, 727, 712, 697 cm^{-1}; MS (ESI): *m/z* (%): 807 (27) $[M_2+H]^+$, 404 (100) $[M+H]^+$, 244 (5), 101 (8); HRMS (ESI): *m/z* calcd for $[C_{21}H_{30}N_3O_5]^+$: 404.2180 $[M+H]^+$; found: 404.2181.

*Dibenzyl-1-((2-benzyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6g**)*

Dibenzyl-1-((2-benzyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to methods A (t_1=14 h, t_2=16 h) and B (t_3=20 h). In method B, CH_2Cl_2 (25 mL) and a flask were used instead of an NMR tube. In method A, compound **1c** (81.7 mg, 470 μmol), enophile **Ed** (155 mg, 521 μmol), and $[Ph_3PAuNTf_2]$ (17.4 mg, 23.5 μmol) were used. In method B, compound **1c** (206 mg, 1.19 mmol), enophile **Ed** (385 mg, 1.29 mmol), and $[Ph_3PAuNTf_2]$ (44.0 mg, 59.5 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 2:1) afforded compound **6g** (method A: 113 mg, 240 μmol, 51%; method B: 495 mg, 1.05 mmol, 88%) as a colorless oil.

R_f (petroleum ether/EtOAc, 2:1): 0.14; ^{1}H NMR (300 MHz, CD_2Cl_2): δ= 3.99 (s, 2H), 4.69 (s, 2H), 5.14 (s, 4H), 6.81 (s, 1H), 7.22–7.33 ppm (m, 15H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=34.8 (t), 44.4 (t), 68.0 (t), 68.7 (t), 125.3 (d), 126.2 (d), 127.1 (d, 2C), 127.2 (d, 2C), 127.4 (d), 127.5 (d), 127.7 (d, 4C), 127.8 (d, 2C), 128.0 (d, 2C), 134.8 (s), 135.1 (s, 2C), 146.3 (s), 154.8 (s), 162.6 (s), 170.1 ppm (s); IR (film): $\tilde{\nu}$=3032, 1721, 1561, 1497, 1454, 1410, 1349, 1264, 1221, 1194, 1111, 1049, 1029, 1001, 975, 733, 697, 645, 576, 504 cm^{-1}; MS (FAB(+)): *m/z* (%): 562 (8), 472 (100) $[M+H]^+$; HRMS (FAB(+)): *m/z* calcd for $[C_{27}H_{26}N_3O_5]^+$: 472.1872 $[M+H]^+$; found: 472.1915.

*Diethyl-1-((2-(thiophen-2-yl)oxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6h**)*

Diethyl-1-((2-(thiophen-2-yl)oxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to methods A (t_1=1 h, t_2=2 h) and B (t_3=3 h). In method A, compound **1d** (45.3 mg, 274 μmol), enophile **Ea** (59.6 mg, 342 μmol), and $[Ph_3PAuNTf_2]$ (10.8 mg, 14.6 μmol) were used. In method B, compound **1d** (28.4 mg, 172 μmol), enophile **Ea** (43.7 mg, 251 μmol), and $[Ph_3PAuNTf_2]$ (6.35 mg, 8.59 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 2:1) afforded compound **6h** (method A: 91.0 mg, 268 μmol, 98%; method B: 56.0 mg, 165 μmol, 96%) as a colorless oil.

R_f (petroleum ether/EtOAc, 2:1): 0.16; ^{1}H NMR (300 MHz, CD_2Cl_2): δ= 1.25 (s, 6H), 4.08–4.21 (m, 4H), 4.72 (s, 2H), 6.63–6.88 (brs, 1H), 6.99 (s, 1H), 7.08 (dd, ^3J=4.8 Hz, ^3J=3.0 Hz, 1H), 7.42 (d, ^3J=4.8 Hz, 1H), 7.58 ppm (d, ^3J=3.0 Hz, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=13.4 (q), 13.6 (q), 43.7 (t), 61.4 (t), 62.2 (t), 126.4 (d), 126.9 (d), 127.2 (d), 127.6

(d), 129.0 (s), 146.1 (s), 155.0 (s), 157.2 ppm (s, 2C); IR (film): $\tilde{\nu}$=3294, 2982, 1717, 1584, 1507, 1493, 1468, 1425, 1382, 1266, 1197, 1121, 1095, 1060, 1020, 987, 853, 764, 726, 711 cm^{-1}; MS (FAB(+)): *m/z* (%): 340 (100) $[M+H]^+$, 266 (6), 261 (4), 251 (6), 250 (7); HRMS (FAB(+)): *m/z* calcd for $[C_{14}H_{18}N_3O_5S]^+$: 340.0967 $[M+H]^+$; found: 340.0923; elemental analysis calcd (%) for $C_{14}H_{17}N_3O_5S$: C 49.55, N 12.38, H 5.05, S 9.45; found C 49.49, N 11.89, H 5.26, S 9.30.

*Diisopropyl-1-((2-(thiophen-2-yl)oxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6i**)*

Diisopropyl-1-((2-(thiophen-2-yl)oxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to methods A (t_1=1 h, t_2=10 h) and B (t_3=13 h). In method A, compound **1d** (35.9 mg, 217 μmol), enophile **Eb** (52.4 mg, 259 μmol), and $[Ph_3PAuNTf_2]$ (8.60 mg, 11.6 μmol) were used. In method B, compound **1d** (26.2 mg, 159 μmol), enophile **Eb** (46.0 mg, 227 μmol), and $[Ph_3PAuNTf_2]$ (5.48 mg, 7.42 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 2:1) afforded compound **6i** (method A: 76.0 mg, 207 μmol, 95%; method B: 58.0 mg, 158 μmol, 99%) as a colorless solid.

M.p.: 2 °C; R_f (petroleum ether/EtOAc, 2:1): 0.25; ^{1}H NMR (500 MHz, CD_2Cl_2): δ=1.24 (s, 12H), 4.71 (s, 2H), 4.80–4.95 (m, 2H), 6.86 (s, 1H), 7.00 (s, 1H), 7.09 (dd, ^3J=5.0 Hz, ^3J=3.0 Hz, 1H), 7.43 (d, ^3J=5.0 Hz, 1H), 7.59 ppm (d, ^3J=3.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ=22.1 (q, 2C), 22.2 (q, 2C), 45.4 (t), 70.2 (d), 71.1 (d), 127.5 (d), 128.0 (d), 128.3 (d), 128.7 (d), 130.3 (s), 147.4 (s), 155.8 (s), 158.3 ppm (s, 2C); IR (film): $\tilde{\nu}$=3289, 3119, 2983, 2360, 2305, 2196, 1713, 1493 , 1468, 1426, 1407, 1386, 1376, 1341, 1316, 1267, 1203, 1181, 1145, 1108, 1041, 990, 955, 711, 678 cm^{-1}; MS (FAB(+)): *m/z* (%): 340 (100) $[M+H]^+$, 266 (6), 261 (4), 251 (6), 250 (7); HRMS (FAB(+)): *m/z* calcd for $[C_{16}H_{21}N_3O_5S]^+$: 368.1280 $[M+H]^+$; found: 368.1248; elemental analysis calcd (%) for $C_{16}H_{21}N_3O_5S$: C 52.30, H 5.76, N 11.44, S 8.73; found: C 52.39, H 5.87, N 11.25, S 9.02.

*Di-tert-butyl-1-((2-(thiophen-2-yl)oxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6j**)*

Di-*tert*-butyl-1-((2-(thiophen-2-yl)oxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to methods A (t_1=1 h, t_2=1 d) and B (t_3=40 h). In method A, compound **1d** (45.3 mg, 274 μmol), enophile **Ec** (59.6 mg, 342 μmol), and $[Ph_3PAuNTf_2]$ (10.8 mg, 14.6 μmol) were used. In method B, compound **1d** (28.3 mg, 171 μmol), enophile **Ec** (56.5 mg, 245 μmol), and $[Ph_3PAuNTf_2]$ (8.37 mg, 11.3 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 2:1) afforded compound **6j** (method A: 91.0 mg, 268 μmol, 98%; method B: 58.0 mg, 147 μmol, 86%) as a colorless solid.

M.p.: 149 °C; R_f (petroleum ether/EtOAc, 2:1): 0.25; ^{1}H NMR (300 MHz, CD_2Cl_2): δ=1.43 (s, 9H), 1.47 (s, 9H), 4.66 (s, 2H), 6.59 (s, 1H), 7.00 (s, 1H), 7.10 (dd, ^3J=5.1 Hz, ^3J=3.9 Hz, 1H), 7.43 (dd, ^3J=5.1 Hz, ^4J=1.2 Hz, 1H), 7.61 ppm (dd, ^3J=3.9 Hz, ^4J=1.2 Hz, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=28.3 (q, 6C), 44.1 (t), 81.6 (s), 82.2 (s), 127.3 (d), 127.9 (d), 128.3 (d), 128.6 (d), 129.7 (s), 130.45 (s), 147.9 (s), 155.2 (s), 158.2 ppm (s); IR (film): $\tilde{\nu}$=3311, 2980, 2933, 1715, 1507, 1493, 1478, 1456, 1425, 1394, 1368, 1320, 1277, 1255, 1154, 1051, 989, 955, 853, 760, 712, 678 cm^{-1}; MS (ESI): *m/z* (%): 396 (100) $[M+H]^+$, 305 (4), 101 (2); HRMS (ESI): *m/z* calcd for $[C_{18}H_{26}N_3O_5S]^+$: 396.1588 $[M+H]^+$; found: 396.1595; elemental analysis calcd (%) for $C_{18}H_{25}N_3O_5S$: C 54.67, H 6.37, N 10.63, S 8.11; found: C 54.64, H 6.40, N 10.35, S 7.85.

*Diethyl-1-((2-cyclopropyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6k**)*

Diethyl-1-((2-*tert*-butyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to methods A (t_1=10 h, t_2=2 d) and B (t_3=3 d). In method A, compound **1e** (42.7 mg, 347 μmol), enophile **Ea** (71.3 mg, 574 μmol), and $[Ph_3PAuNTf_2]$ (13.2 mg, 17.9 μmol) were used. In method B, compound **1e** (40.2 mg, 327 μmol), enophile **Ea** (84.4 mg, 485 μmol), and $[Ph_3PAuNTf_2]$ (12.6 mg, 17.0 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 1:1) afforded compound **6k** (method A: 55.0 mg, 185 μmol, 53%); method B: 64.0 mg, 215 μmol, 66%) as a colorless oil.

R_f (petroleum ether/EtOAc, 2:1): 0.17; ^{1}H NMR (300 MHz, CD_2Cl_2): δ=0.95 (s, 2H), 0.97 (s, 2H), 1.07–1.25 (m, 6H), 1.98 (s, 1H), 4.07–4.20 (m, 4H), 4.59 (s, 2H), 6.72 (s, 1H), 7.45 ppm (s, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=7.1 (t, 2C), 7.9 (d), 13.4 (q), 13.5 (q), 42.9 (t), 62.0 (t), 62.2 (t), 124.9 (d), 145.3 (s), 155.1 (s), 165.6 (s), 170.2 ppm (s); IR (film): $\tilde{\nu}$=3290, 2984, 2937, 1719, 1572, 1518, 1468, 1421, 1383, 1349, 1303, 1262, 1201, 1139, 1096, 1061, 1030, 992, 765, 732 cm^{-1}; MS (ESI): *m/z* (%): 595 (9) $[M_2+H]^+$, 542 (37), 493 (31), 393 (100), 298 (30) $[M+H]^+$, 108 (5), 101 (5), 96 (4); HRMS (ESI): *m/z* calcd for $[C_{13}H_{20}N_3O_5]^+$: 298.1398 $[M+H]^+$; found: 298.1398.

*Di-tert-butyl-1-((2-adamantyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6l**)*

Di-*tert*-butyl-1-((2-adamantyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate was prepared according to method B (t_3=45 h). Compound **1g** (105 mg, 483 μmol), enophile **Ec** (121 mg, 525 μmol), and $[Ph_3PAuNTf_2]$ (12.9 mg, 17.4 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 2:1) afforded compound **6l** (183 mg, 409 μmol, 85%) as a colorless solid.

R_f (petroleum ether/EtOAc, 2:1): 0.44; ^{1}H NMR (300 MHz, CD_2Cl_2): δ=1.42 (s, 18H), 1.76 (s, 6H), 1.99 (m, 6H), 2.06 (brs, 3H), 4.57 (s, 2H), 6.55 (brs, 1H), 6.79 ppm (s, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=28.3 (q, 6C), 28.5 (d, 3C), 36.0 (s), 36.8 (t, 3C), 40.7 (t, 3C), 60.6 (t), 81.5 (s), 81.9 (s), 125.3 (d), 147.0 (s), 155.13 (s), 177.2 (s), 177.3 ppm (s); IR (film): $\tilde{\nu}$=3311, 3199, 2979, 2909, 2853, 1731, 1551, 1478, 1454, 1393, 1368, 1346, 1313, 1275, 1254, 1155, 1120, 1103, 1052, 996, 956, 712 cm^{-1}; MS (ESI): *m/z* (%): 933 (2) $[M_2+K]^+$, 917 (6) $[M_2+Na]^+$, 895 (3) $[M_2+H]^+$, 486 (22) $[M+K]^+$, 470 (47) $[M+Na]^+$, 448 (100) $[M+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{24}H_{38}N_3O_5]^+$: 448.2806 $[M+H]^+$; found: 448.2809.

*1-((2-tert-Butyloxazol-5-yl)methyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**7a**)*

1-((2-*tert*-Butyloxazol-5-yl)methyl)-4-phenyl-1,2,4-triazolidine-3,5-dione was prepared according to methods A (t_1=0.5 h, t_2=1.5 h) and B (t_3=3 d). In method A, compound **1b** (39.6 mg, 284 μmol), enophile **Ee** (54.1 mg, 309 μmol), and $[Ph_3PAuNTf_2]$ (6.47 mg, 8.75 μmol) were used. In method B, compound **1b** (20.1 mg, 144 μmol), enophile **Ee** (33.4 mg, 191 μmol), and $[Ph_3PAuNTf_2]$ (4.52 mg, 6.11 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 1:4) afforded compound **7a** (method A: 79.5 mg, 253 μmol, 89%; method B: 21.0 mg, 66.8 μmol, 46%) as a yellow oil.

R_f (petroleum ether/EtOAc, 1:2): 0.17; ^{1}H NMR (300 MHz, CD_2Cl_2): δ=1.30 (s, 9H), 4.73 (s, 2H), 6.92 (s, 1H), 7.38–7.52 ppm (m, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=28.6 (q, 3C), 34.2 (s), 42.5 (t), 126.1 (d, 2C), 126.4 (d), 128.8 (d), 129.5 (d, 2C), 131.7 (s), 145.1 (s), 154.2 (s), 172.8 ppm (s, 2C); IR (film): $\tilde{\nu}$=3318, 3213, 2978, 2934, 2873, 1718, 1556, 1478, 1458, 1393, 1368, 1253, 1154, 1050, 1022, 994, 957, 859, 742, 705 cm^{-1}; MS (FAB(+)): *m/z* (%): 315 (100) $[M+H]^+$, 314 (18), 289 (5), 283 (6), 282 (10), 281 (31), 279 (26), 267 (15), 261 (13), 239 (5), 221 (29); HRMS (FAB(+)): *m/z* calcd for $[C_{16}H_{19}N_4O_3]^+$: 315.1457 $[M+H]^+$; found: 315.1476.

*1-((2-Benzyloxazol-5-yl)methyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**7b**)*

1-((2-Benzyloxazol-5-yl)methyl)-4-phenyl-1,2,4-triazolidine-3,5-dione was prepared according to methods A (t_1=14 h, t_2=1.5 h) and B (t_3=4 d). In method A, compound **1c** (35.6 mg, 206 μmol), enophile **Ee** (37.3 mg, 213 μmol), and $[Ph_3PAuNTf_2]$ (4.56 mg, 6.17 μmol) were used. In method B, compound **1c** (58.9 mg, 3.40 μmol), enophile **Ee** (60.1 mg, 343 μmol), and $[Ph_3PAuNTf_2]$ (13.4 mg, 18.1 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 1:2) afforded compound **7b** (method A: 16.0 mg, 45.9 μmol, 22%; method B: 49.0 mg, 141 μmol, 41%) as a dark-yellow oil.

R_f (petroleum ether/EtOAc, 1:2): 0.21; ^{1}H NMR (300 MHz, CD_2Cl_2): δ=4.04 (s, 2H), 4.69 (s, 2H), 6.23 (brs, 1H), 7.20–7.35 (m, 5H), 7.37–7.51 ppm (m, 5H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=33.7 (t), 41.2 (t), 124.9 (d, 2C), 125.8 (d), 126.4 (d), 127.6 (d), 127.9 (d, 2C),128.0 (d, 2C), 128.3 (d, 2C), 130.5 (s), 134.4 (s), 147.7 (s), 152.9 (s), 153.0 (s), 163.5 ppm (s); IR (film): $\tilde{\nu}$=3064, 3032, 2924, 1773, 1713, 1600, 1560, 1502, 1455,

1423, 1359, 1262, 1111, 997, 955, 770, 729, 711, 696, 638 cm^{-1}; MS (FAB(+)): *m/z* (%): 349 (83) $[M+H]^+$, 347 (66), 326 (11), 307 (12), 305 (15), 289 (17), 281 (17), 279 (21), 136 (100); HRMS (FAB(+)): *m/z* calcd for $[C_{19}H_{17}N_4O_3]^+$: 349.2301 $[M+H]^+$; found: 349.1287.

*4-Phenyl-1-((2-(thiophen-2-yl)oxazol-5-yl)methyl)-1,2,4-triazolidine-3,5-dione (**7c**)*

4-Phenyl-1-((2-(thiophen-2-yl)oxazol-5-yl)methyl)-1,2,4-triazolidine-3,5-dione was prepared according to methods A ($t_1=1$ h, $t_2=2$ h) and B ($t_3=11$ d). In method A, compound **1d** (34.6 mg, 209 μmol), enophile **Ee** (37.0 mg, 211 μmol), and $[Ph_3PAuNTf_2]$ (7.50 mg, 10.1 μmol) were used. In method B, compound **1d** (50.1 mg, 303 μmol), enophile **Ee** (53.5 mg, 305 μmol), and $[Ph_3PAuNTf_2]$ (11.0 mg, 14.9 μmol) were used. Column chromatography on silica gel (petroleum ether/EtOAc, 1:1) afforded compound **7c** (method A: 29.0 mg, 85.2 μmol, 41%; method B: 51.0 mg, 150 μmol, 49%) as a colorless solid.

M.p.: 163 °C; R_f (petroleum ether/EtOAc, 1:1): 0.24; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta=4.84$ (s, 2H), 7.22 (dd, $^3J=5.1$ Hz, $^3J=3.6$ Hz, 1H), 7.32 (s, 1H), 7.38–7.54 (m, 6H), 7.69 (dd, $^3J=3.6$ Hz, $^4J=1.2$ Hz, 1H), 7.80 ppm (dd, $^3J=5.1$ Hz, $^4J=1.2$ Hz, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): $\delta=41.8$ (t), 126.5 (d, 2C), 128.2 (d), 128.4 (d), 128.5 (d), 128.9 (d), 129.2 (s), 129.3 (d, 2C), 130.1 (d), 131.9 (s), 146.0 (s), 153.1 (s), 154.0 (s), 157.7 ppm (s); IR (KBr): $\tilde{\nu}=3432$, 3117, 2926, 1708, 1627, 1542, 1502, 1454, 1419, 1311, 1255, 1134, 1047, 767, 728, 693, 646, 617, 583, 508 cm^{-1}; MS (FAB(+)): *m/z* (%): 413 (100), 363 (18), 341 (50) $[M+H]^+$, 331 (5), 279 (4); HRMS (FAB(+)): *m/z* calcd for $[C_{16}H_{13}N_4O_3S]^+$: 341.0708 $[M+H]^+$.

*6-tert-Butyl-5-oxa-7-azaspiro[3.4]oct-6-ene-1,1,2,2-tetracarbonitrile (**8**)*

To a solution of compound **1b** (105 mg, 750 mmol) in CH_2Cl_2 (20 mL), was added catalyst $[Ph_3PAuNTf_2]$ (28.7 mg, 38.8 μmol). After 1.5 h, the mixture was cooled to −40 °C. Tetracyanoethylene enophile **Ef** (110 mg, 859 mol) was added dropwise and the resulting solution was stirred at −40 °C for 2 h, before being slowly warmed to room temperature. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 3:1) to furnish compound **8** (91.0 mg, 340 μmol, 45%) as a brown solid.

M.p.: 126 °C (dec.); R_f (petroleum ether/EtOAc, 2:1): 0.38; ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta=1.27$ (s, 9H), 3.44 (d, $^2J=14.1$, 1H), 3.63 (d, $^2J=14.1$, 1H), 4.09 (d, $^2J=17.1$, 1H), 4.55 ppm (d, $^2J=17.1$, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): $\delta=27.5$ (s), 27.8 (q, 3C), 32.0 (s), 34.2 (s), 45.4 (t), 64.8 (t), 85.51 (s), 108.0 (s), 108.9 (s), 110.7 (s), 111.0 (s), 173.0 ppm (s); IR (KBr): $\tilde{\nu}=3444$, 3025, 2976, 2933, 2874, 1691, 1637, 1601, 1557, 1482, 1461, 1427, 1368, 1285, 1229, 1112, 1037, 1007, 920, 855 cm^{-1}; MS (EI(+), 70 eV): *m/z* (%): 268 $[M+H]^+$ (8), 241 (7), 236 (6), 110 (6), 108 (11), 101 (7), 96 (4), 89 (5); HRMS (EI(+), 70 eV): *m/z* calcd for $[C_{14}H_{14}N_5O]^+$: 268.1193 $[M+H]^+$; found: 268.1196.

*Comparison of Different Au^I CatalystsDi-tert-butyl-1-((2-benzyloxazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (**6f**)*

In an NMR tube, compound **1c**, enophile **Ec**, and 1,3,5-tri-*tert*-butylbenzol (2 mg) as a standard were dissolved in CD_2Cl_2 (600 μL) and the catalyst was added (Table 4). The yield was determined by ^{1}H NMR spectroscopy.

Table 4. Comparison of different catalysts for the reaction of compound **1c** to form compound **6f**.

Reactant **1c**	Enophile **Ec**	Catalyst	Yield [%]
18.8 mg, 109 μmol	26.3 mg, 114 μmol	$[Ph_3PAuNTf_2]$ (1.61 mg, 2.18 μmol)	84
16.4 mg, 94.7 μmol	22.9 mg, 99.4 μmol	**K1** (1.54 mg, 1.62 μmol)	92
14.0 mg, 80.8 μmol	19.5 mg, 84.7 μmol	**K2** (1.84 mg, 1.87 μmol)	98

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (HA 1932/11-1). We thank Umicore AG & Co. KG for the generous donation of noble-metal salts.

[1] a) D. C. Palmer, S. Venkatraman in *The Chemistry of Heterocyclic Compounds, A Series of Monographs, Oxazoles: Synthesis Reactions, and Spectroscopy, Part A* (Ed.: D. C. Palmer), Wiley, New York, **2003**; b) S. Lang-Fugmann in *Methoden der Organischen Chemie (Houben-Weyl)* (Ed.: E. Schaumann), Thieme, Stuttgart, **1993**; c) R. Lakhan, B. Ternai, *Adv. Heterocycl. Chem.* **1974**, *17*, 99–211; d) G. J. Pattenden, *Heterocycl. Chem.* **1992**, *29*, 607–618.

[2] For the most-recent examples, see: a) T. Doi, K. Shibata, M. Yoshida, M. Takagi, M. Tera, K. Nagasawa, K. Shin-ya, T. Takahashi, *Org. Biomol. Chem.* **2011**, *9*, 387–393; b) M. P. DeNinno, S. W. Wright, M. S. Visser, J. B. Etienne, D. E. Moore, T. V. Olson, B. N. Rocke, M. P. Andrews, C. Zarbo, M. L. Millham, B. P. Boscoe, D. D. Boyer, S. D. Doran, K. L. Houseknecht, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3095–3098; c) S. Majima, M. Tera, K. Iida, K. Shin-ya, K. Nagasawa, *Heterocycles* **2011**, *82*, 1345–1357; d) W. Zhang, W. Liu, X. Jiang, F. Jiang, H. Zhuang, L. Fu, *Eur. J. Med. Chem.* **2011**, *46*, 3639–3650; e) B. Kalyon, S. E. Helaly, R. Scholz, J. Nachtigall, J. Vater, R. Borriss, R. D. Süssmuth, *Org. Lett.* **2011**, *13*, 2996–2999.

[3] For the most-recent examples, see: a) C.-Y. Chen, T. Andreani, H. Li, *Org. Lett.* **2011**, *13*, 6300–6303; b) A. J. Morrison, J. M. Adam, J. A. Baker, R. A. Campbell, J. K. Clark, J. E. Cottney, M. Deehan, A.-M. Easson, R. Fields, S. Francis, F. Jeremiah, N. Keddie, T. Kiyoi, D. R. McArthur, K. Meyer, P. D. Ratcliffe, J. Schulz, G. Wishart, K. Yoshiizumi, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 506–509; c) J.-I. Kuroyanagi, K. Kanai, Y. Sugimoto, T. Horiuchi, I. Achiwa, H. Takeshita, K. Kawakami, *Bioorg. Med. Chem.* **2010**, *18*, 7593–7606; d) F. Hamon, E. Largy, A. Guédin-Beaurepaire, M. Rouchon-Dagois, A. Sidibe, D. Monchaud, J.-L. Mergny, J.-F. Riou, C.-H. Nguyen, M.-P. Teulade-Fichou, *Angew. Chem.* **2011**, *123*, 8904–8908; *Angew. Chem. Int. Ed.* **2011**, *50*, 8745–8749; for one of the most-prominent examples of an oxazole with a longer alkyl chain at the 5-position, see: e) B. Kunze, R. Janssen, G. Höfle, H. Reichenbach, *J. Antibiot.* **2004**, *57*, 151–155.

[4] a) R. Robinson, *J. Chem. Soc.* **1909**, *95*, 2167–2174; b) S. Gabriel, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 134–138; c) S. Gabriel, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1283–1287; d) E. Fischer, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 205–214; e) H. Bredereck, R. Gompper, *Chem. Ber.* **1954**, *87*, 700–707; f) H. Bredereck, R. Bangert, *Chem. Ber.* **1964**, *97*, 1414–1423; g) A. M. van Leusen, B. E. Hoogenboom, H. Siderius, *Tetrahedron Lett.* **1972**, *13*, 2369–2372; h) B. A. Kulkarnia, A. Ganesan, *Tetrahedron Lett.* **1999**, *40*, 5637–5638.

[5] G. Theilig, *Ber. Dtsch. Chem. Ges.* **1953**, *86*, 96–109.

[6] a) Y. Yura, *Chem. Pharm. Bull.* **1962**, *10*, 1087–1093; b) K. E. Schulte, J. Reisch, M. Sommer, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1966**, *299*, 107–112; c) F. Eloy, A. Deryckere, *Chim. Ther.* **1973**, *8*, 437–446; d) L. J. Street, R. Baker, J. L. Castro, M. S. Chambers, A. R. Guiblin, S. C. Hobbs, V. G. Matassa, A. J. Reeve, M. S. Beer, *J. Med. Chem.* **1993**, *36*, 1529–1538.

[7] a) B. M. Nilsson, U. Hacksell, *J. Heterocycl. Chem.* **1989**, *26*, 269–275; b) B. M. Nilsson, H. M. Vargas, B. Ringdahl, U. Hacksell, *J. Med. Chem.* **1992**, *35*, 285–294.

[8] a) L. E. Overman, S. Tsuboi, S. Angle, *J. Org. Chem.* **1979**, *44*, 2323–2325; b) L. E. Overman, J. P. Roos, *J. Org. Chem.* **1981**, *46*, 811–813.

[9] A. Arcadi, S. Cacchi, L. Cascia, G. Fabrizi, F. Marinelli, *Org. Lett.* **2001**, *3*, 2501–2504.

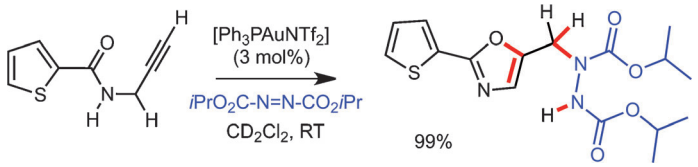
[10] A. Bacchi, M. Costa, B. Gabriele, G. Pelizzi, G. Salerno, *J. Org. Chem.* **2002**, *67*, 4450–4457.

[11] a) E. Merkul, T. J. J. Müller, *Chem. Commun.* **2006**, 4817–4819; b) E. Merkul, O. Grotkopp, T. J. J. Müller, *Synthesis* **2009**, 502–507; c) E. M. Beccalli, E. Borsini, G. Broggini, G. Palmisano, S. Sottocor-

nola, *J. Org. Chem.* **2008**, *73*, 4746–4749; d) M. Harmata, C. Huang, *Synlett* **2008**, 1399–1401.
[12] A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391–4394.
[13] a) D. Aguilar, M. Contel, R. Navarro, T. Soler, P. E. Urriolabeitia, *J. Organomet. Chem.* **2009**, *694*, 486–493; b) G. Verniest, A. Padwa, *Org. Lett.* **2008**, *10*, 4379–4382.
[14] a) D. Dorsch, L. T. Burgdorf, R. Gericke, N. Beier, W. Mederski, WO 2005123688A2, **2005**; [*Chem. Abstr.* **2005**, *144*, 69837]; b) D. Dorsch, O. Schadt, A. Blaukat, F. Stieber, WO 2008/017361A2, **2008**; [*Chem. Abstr.* **2008**, *148*, 190536].
[15] M. D. Milton, Y. Inada, Y. Nishibayashi, S. Uemura, *Chem. Commun.* **2004**, 2712–2713.
[16] A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus, W. Frey, *Eur. J. Org. Chem.* **2006**, 4905–4909.
[17] a) A. S. K. Hashmi, A. Loos, A. Littmann, I. Braun, J. Knight, S. Doherty, F. Rominger, *Adv. Synth. Catal.* **2009**, *351*, 576–582; b) S. Doherty, J. G. Knight, A. S. K. Hashmi, C. H. Smyth, N. A. B. Ward, K. J. Robson, S. Tweedley, R. W. Harrington, W. Clegg, *Organometallics* **2010**, *29*, 4139–4147; c) A. S. K. Hashmi, A. Loos, S. Doherty, J. G. Knight, K. J. Robson, F. Rominger, *Adv. Synth. Catal.* **2011**, *353*, 749–759; d) A. S. K. Hashmi, C. Lothschütz, K. Graf, T. Häffner, A. Schuster, F. Rominger, *Adv. Synth. Catal.* **2011**, *353*, 1407–1412; e) A. S. K. Hashmi, A. M. Schuster, M. Schmuck, F. Rominger, *Eur. J. Org. Chem.* **2011**, 4595–4602; f) A. S. K. Hashmi, A. M. Schuster, S. Gaillard, L. Cavallo, A. Poater, S. P. Nolan, *Organometallics* **2011**, *30*, 6328–6337.
[18] The tolerance to water and oxygen has already been reported in earlier works on gold catalysis, see: a) Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729–3731; b) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem.* **1998**, *110*, 1475–1478; *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418; c) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382–2385; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285–2288; d) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554.
[19] A. S. K. Hashmi, A. M. Schuster, S. Litters, F. Rominger, M. Pernpointner, *Chem. Eur. J.* **2011**, *17*, 5661–5667.
[20] G. Capozzi, C. Caristi, M. Gattuso, G. S. d'Alcontres, *Tetrahedron Lett.* **1981**, *22*, 3325–3328.
[21] G. Capozzi, C. Caristi, M. Gattuso, *J. Chem. Soc. Perkin Trans. 1* **1984**, 255–260.
[22] a) A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *J. Organomet. Chem.* **2009**, *694*, 592–597; b) A. S. K. Hashmi, T. Dondeti Ramamurthi, M. H. Todd, A. S.-K. Tsang, K. Graf, *Aust. J. Chem.* **2010**, *63*, 1619–1626; see also first observations in: c) A. S. K. Hashmi, M. C. Blanco, D. Fischer, J. W. Bats, *Eur. J. Org. Chem.* **2006**, 1387–1389.
[23] J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, W. Frey, J. W. Bats, *Chem. Eur. J.* **2010**, *16*, 956–963.
[24] N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136.
[25] C. Khin, A. S. K. Hashmi, F. Rominger, *Eur. J. Inorg. Chem.* **2010**, 1063–1069.
[26] a) D. A. Evans, S. G. Nelson, *J. Am. Chem. Soc.* **1997**, *119*, 6452–6453; b) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656-5657; c) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868–1871; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790–1793.

Received: January 13, 2012
Revised: February 18, 2012
Published online: ■■ ▮▮, 0000

FULL PAPERS



The famous five: The one-pot reaction of readily available *N*-propargylamides and azodicarboxylates provided functionalized oxazoles through a five-step cycloisomerization/Alder-ene reaction pathway.

Oxazoles

*A. Stephen K. Hashmi,**
Anna Littmann ——— ■■■■–■■■■

Gold Catalysis: One-Pot Alkylidene-neoxazoline Synthesis/Alder-Ene Reaction