Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801386

Link to VoR: http://dx.doi.org/10.1002/adsc.201801386

10.1002/adsc.201801386

FULL PAPER

DOI: 10.1002/adsc.201801386

Gold-Catalyzed Synthesis of 2,5-Disubstituted Oxazoles from Carboxamides and Propynals

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Received: ((will be filled in by the editorial staff))

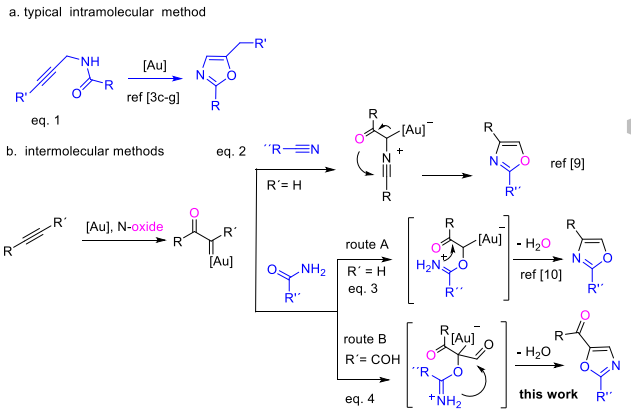
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. 2,5-Disubstituted oxazoles are synthesized by oxidative gold catalysis. In contrast to a reported procedure that delivers 2,4-disubstituted oxazoles starting from terminal alkynes, a switch in selectivity towards a 2,5-disubstitution is achieved by the use of propynals as starting materials. In the new reaction, the key intermediate is formed by the nucleophilic attack of the carboxamide onto a gold carbenoid, and then condensates with the more electrophilic aldehyde moiety already present in the substrate and not by the ketone that is derived from the oxygen donor. This new cyclization mode introduces a new carbonyl moiety as substituent at the 2,5-disubstituted oxazole, an attractive motive that can be found in bioactive compounds or be used for further derivatizations.

Keywords: gold catalysis; gold carbenoids; carboxamides; *N*-oxides; oxazoles

Introduction

2,5-Disubstituted oxazoles exhibit extremely valuable properties, and they are found as an important motif in bioactive compounds[1] and pharmaceuticals.[2] As a consequence, a large number of intramolecular strategies towards these targets were established in the last decades[3] (Scheme 1, eq. 1). In order to increase the modularity of the synthetic protocols, efficient intermolecular methods to access 2,5-substituted oxazoles are desirable. For this purpose, many metal catalysts were applied, such as copper,[4] palladium,[5] ruthenium[6] and cobalt.[7] In the field of gold catalysis[8] an elegant strategy was introduced by Zhang's group in which intermediary formed α-oxo gold carbene intermediates, generated by *N*-oxides,[9] were trapped by nitriles to form 2,5-disubstituted oxazoles via an intermolecular process (Scheme 1, eq. 2).[10] The drawback of this protocol is the need for at least 3 equivalents of the nitrile or its use as reaction solvent. If carboxamides were used as nucleophiles in combination with adjusted ligands at the gold center, better ratios of the two reactants were possible. In this case 2,4-disubstituted oxazoles are formed by condensation of the amide unit with the carbonyl moiety derived from the *N*-oxide and the terminal alkyne (Scheme 1, eq. 3).[11] Based on these reports we envisioned that if propynals were used as α-oxo gold carbene precursors a different pathway might be opened. As depicted in Scheme 1 (eq. 4), the additional, more active carbonyl moiety should condensate with the amide moiety, which instead of 2,4-oxazoles should deliver 2,5-oxazoles. Related methods for gold-catalyzed oxidative cyclization of yones were reported in previous studies.[12]



Scheme 1. Gold-catalyzed strategies towards oxazoles

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For this type of substrates, the oxygen transferred from the *N*-oxide should remain in the obtained products. This should enable a more efficient access to 2,5-disubstituted oxazoles which in addition bear one carbonyl unity as substituent. These are valuable substructures which can be found in bioactive compounds such as fura-2 acetoxymethyl ester[13] and ACC1 inhibitors (Figure 1).[14] The results on this project are summarized herein.

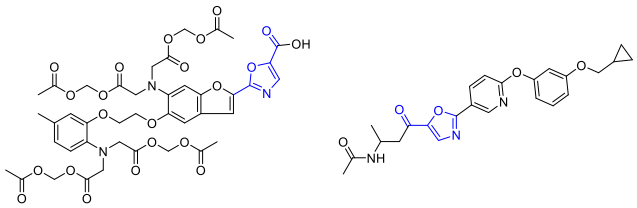
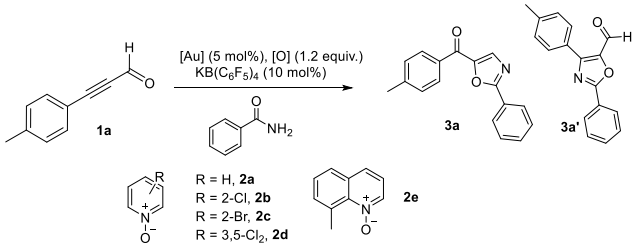


Figure 1. Bioactive oxazoles

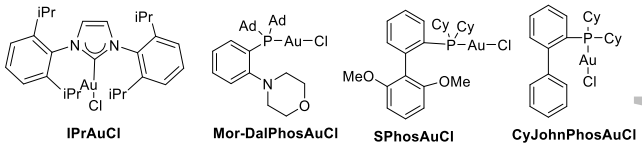
Results and Discussion

Table 1. Optimization of the reaction conditions [a,b]



Entry [a]	catalyst	*N*-oxide	Solvent	Yield[b] (%)
1	IPrAuCl	**2d**	1,2-DCE	44
2	Mor-DalPhosAuCl	**2d**	1,2-DCE	50
3	SPhosAuCl	**2d**	1,2-DCE	43
4	$(4\text{-}CF_3C_6H_4)_3PAuCl$	**2d**	1,2-DCE	42
5	CyJohnphosAuCl	**2d**	1,2-DCE	53
6	Ph_3PAuCl	**2d**	1,2-DCE	61
7	$KB(C_6F_5)_4$	**2d**	1,2-DCE	n.r.
8	Ph_3PAuCl	**2a**	1,2-DCE	10
9	Ph_3PAuCl	**2b**	1,2-DCE	43
10	Ph_3PAuCl	**2c**	1,2-DCE	20
11	Ph_3PAuCl	**2d**	1,2-DCE	2
12	Ph_3PAuCl	**2d**	TFE	56
13	Ph_3PAuCl	**2d**	$PhCF_3$	57
14	Ph_3PAuCl	**2d**	1,4-dioxane	20
15	Ph_3PAuCl	**2d**	THF	31
16	Ph_3PAuCl	**2d**	toluene	51
17	Ph_3PAuCl	**2d**	PhCl	71(64)[c]
18	Ph_3PAuCl	**2d**	PhCl	7[d]
19	Ph_3PAuCl	**2d**	PhCl	20[e]
20	Ph_3PAuCl	**2d**	PhCl	41[f]

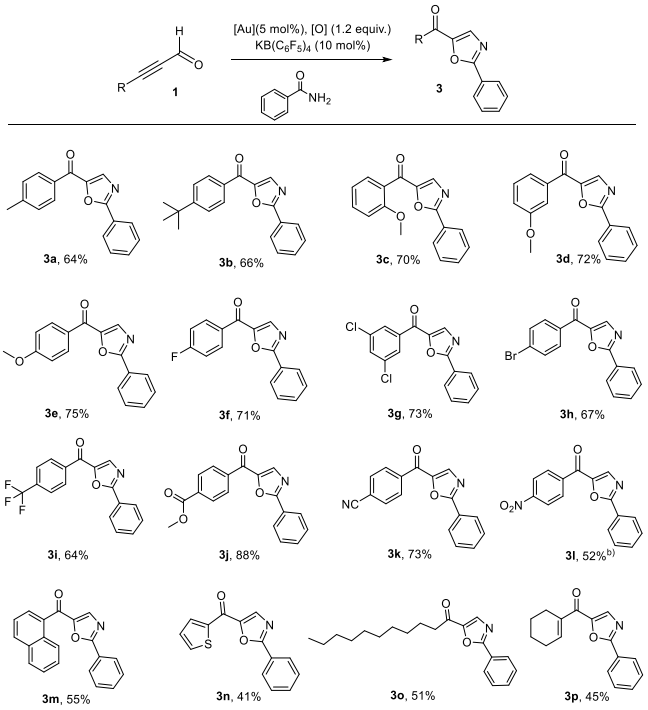
[a] All reactions were carried out on a 0.1 mmol scale in 0.6 ml solvent in presence of 1.2 eq *N*-oxide, 10 mmol% $KB(C_6F_5)_4$ at 80 °C for 24 h. [b] Yield was determined by NMR analysis using CH_2Br_2 as the internal standard. [c] Isolated yield. [c] Isolated yield. [d] $KBPh_4$ was used as additive. [e] $AgSbF_6$ was used as additive. [f] $AgNTf_2$ was used as additive.



Initially, (4-methylphenyl)propynal (**1a**) and benzamide were selected as model substrates for reaction optimizations. In order to get the activated gold species, $KB(C_6F_5)_4$ which has been used as excellent chloride scavenger[15] was chosen to obtain the weakly coordinating anion $B(C_6F_5)_4^-$. To our delight, a first test reaction with pyridine *N*-oxide (**2a**) and IPr as ligand at 80 °C delivered 44% of the desired product in a ratio 3a:3a'>30:1 (entry 1). A series of phosphine ligands was tested, simple PPh_3 delivered a better result (entry 6) than Buchwald-type ligands (entries 3,5), a more electron-deficient simple phosphane ligand (entry 4), or basic Mor-Dal-Phos (entry 2). The control experiment with $KB(C_6F_5)_4$ alone showed no conversion of **1a** (entry 7). After that, a variety of *N*-oxides was tested. Halogen-substituted *N*-oxides showed better yields than simple pyridine *N*-oxide or 8-methylquinoline *N*-oxide (entry 8-11).

$Ph_3PAuCl/KB(C_6F_5)_4$ turned out to be the best catalyst system together with 3,5-dichloropyridine *N*-oxide as oxygen donor. A solvent screening including TFE, $PhCF_3$, 1,4-dioxane, THF, toluene and chlorobenzene showed the best result of 71% (isolated yield 64%) for chlorobenzene (entry 17). Under the optimized conditions, $KBPh_4$, $AgSbF_6$ and $AgNTf_2$ were used as additive to check if they were better than $KB(C_6F_5)_4$ (entry18-20). It was proved that $Ph_3PAuCl/KB(C_6F_5)_4$ was best catalytic system.

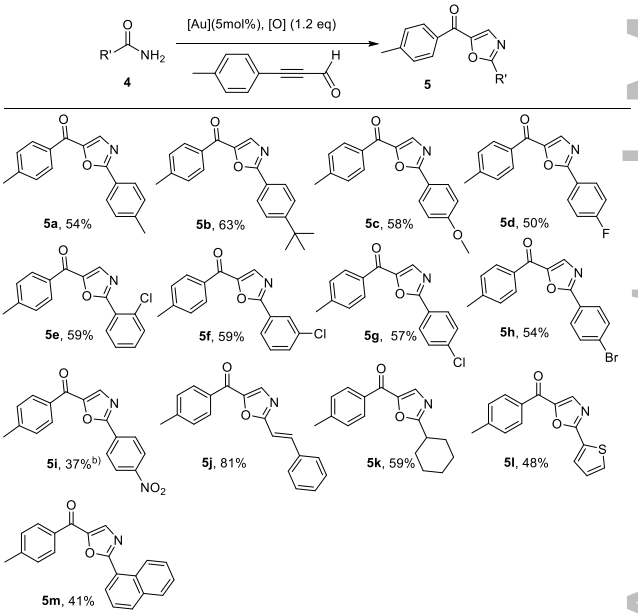
Table 2. Reaction scope with respect to the propynal [a)]



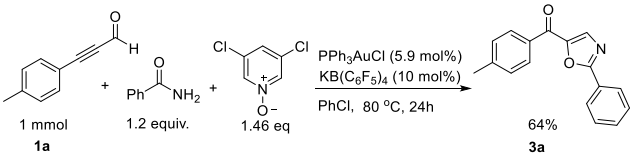
[a)] All reactions were carried out on a 0.2 mmol scale in 1.0 ml solvent in presence of 1.2 eq *N*-oxide, 10 mol% $KB(C_6F_5)_4$ at 80 °C for 24 h. All yields given in this table refer to isolated products. [b)] Reaction time of 36 h.

Under the optimized conditions, the scope with respect to the propynal was investigated first (Table 2). Different substituted aromatic groups at the alkyne terminus were all tolerated well. For electron-donating groups like alkyl (**3a**, **3b**) or methoxy (**3c**-**3e**) no strong influence on yield was observed and all of the corresponding oxazoles were obtained in yields up to 75%. The position of the substituent also plays a minor role, which was tested in the series of *ortho*-, *meta*- and *para*-substituted starting materials (**1c**-**1e**). For electron-withdrawing group at the aromatic moiety similar reactivities and yields were observed. Substrates with varying halogen substituents including fluorides, chlorides and bromides, afforded product **3f**-**3h** in 67-73% yield. Other important functional groups such as trifluoromethyl (**3i**), esters (**3j**), or nitriles (**3k**) also delivered good yields. A drop in yield was observed for nitro substituted compound **1l**. Even under prolonged reaction time of 36 h only 52% of **3l** were obtained. A larger aromatic system (**3m**) and one heterocyclic thiophen substituent **(3n**) delivered the corresponding products in moderate yield. Alkyl- and alkenyl-substituted propynals were also suitable substrates leading to **3o** and **3p** in moderate yield. Next, a series of carboxamides was subjected to the standard reaction conditions (Table 3). In general, both electron-rich and electron-deficient substituents at the aromatic rings were tolerated, affording the desired compounds **5a**-**5i** in 37%-63% yield. Like in Table 2 case, substituent effects turned out to be only marginal for most of the applied starting materials no matter if electron-rich (**5a**-**5c**) or electron-deficient (**5d**-**5h**) substrates were converted. Also in line with the results from Table 2, the position of a substituent on the aromatic moiety did not influence the yield (**5e**-**5g**) but the installation of a nitro group significantly reduced the yield (**5i**). Trans-cinnamamide as alkenyl precursor delivered the best yield (81%) in this series (**5j**). Cyclohexyl amide was also suitable and alkyl substituted oxazole **5k** was obtained in 59% yield. Heterocyclic and other carbocyclic substrates were tested, too. The yields of thienyl (**5l**) or naphthyl (**5m**) oxazole were 48% and 41% respectively. Efforts with the pyridyl-substituted amide failed. An ester instead of an aldehyde at the alkyne part was tested as well but in this case only an unselective reaction was observed which can be explained by the lower electrophilicity of the ester carbonyl.

Table 3. Reaction scope with respect to the amide compound [a)]



[a)] All reactions were carried out on a 0.2 mmol scale in 1.0 ml solvent in presence of 1.2 eq *N*-oxide, 10 mmol% $KB(C_6F_5)_4$ at 80 °C for 24 h;; yields are isolated yields. [b)] Reaction time of 36 h.



Scheme 2. mmol-Scale synthesis of **3a**.

The reaction of **1a** with benzamide could be easily run on 1 mmol scale with a catalyst loading of 5.9 mol%, **3a** was still isolated in 64% yield (Scheme 2).

Conclusion

In summary, a gold-catalyzed pathway towards 2,5-disubstituted oxazoles bearing one acyl substituent was developed. Key for the selectivity switch from the known synthesis of 2,4-disubstituted oxazoles from terminal alkynes and carboxamides, towards the synthesis of 2,5-oxazoles, is the installation of an aldehyde moiety on the alkyne. Due to its higher electrophilicity, compared to the ketone derived from the oxidation of the alkyne, condensation towards the target aromatic system occurs with maintenance of the ketone moiety in the product. Due to the simplicity of the starting materials, this protocol offers an attractive alternative to the existing strategies towards the target molecules.

Experimental Section

A round bottom flask equipped with a magnetic stirrer bar was charged with $(PPh_3)PAuCl$ (5 mol%, 2.47 mg), $KB(C_6F_5)_4$ (10 mol%, 7.2 mg), 3,5-dichloropyridine *N*-oxide (1.2 eq, 19.6 mg), **1a** (0.1 mmol, 14.4 mg), benzamide (0.12 mmol, 14.5 mg) and chlorobenzene (0.6 ml). The mixture was stirred for 24 h at 80 °C. After cooling to room temperature, the solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (eluent: PE/EA=5:1 to 10:1) to afford the product **3a**.

(2-Phenyloxazol-5-yl)(*p*-tolyl)methanone (**3a**)

Yield 64%, light yellow solid, m.p.132-133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20-8.19 (d, J = 6.6 Hz, 2H), 7.93-7.91 (d, J = 8.1 Hz, 2H), 7.86 (s, 1H) 7.56-7.49 (m, 3H), 7.36-7.34 (d, J = 7.9 Hz, 2H), 2.46 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.2 (s), 164.6 (s), 149.1 (s), 144.3 (d), 137.3 (s), 134.3 (s), 131.9 (d), 129.5 (d, 2C), 129.2 (d, 2C), 129.0 (d, 2C), 127.5 (d, 2C), 126.3 (d), 21.76 (q) ppm; IR (ATR): ṽ 2925, 2853, 1649, 1605, 1555, 1523, 1473, 1447, 1355, 1301, 1243, 1153, 1109, 1071, 997, 945, 899, 868, 832, 786, 753, 719, 704, 691, 642, 628; HRMS (ESI) Calcd for $[C_{17}H_{13}NO_2]$ ($[M+H]^+$), 264.1024, found 264.1017.

(4-(*tert*-Butyl)phenyl)(2-phenyloxazol-5-yl)methanone (**3b**)

Yield 66 %, white solid, m.p. 130-131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21-8.19 (d, J = 8.2 Hz, 2H), 7.98-7.96 (d, J = 8.5 Hz, 2H), 7.89 (s, 1H), 7.57-7.50 (m, 5H), 1.38 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.1 (s), 164.6 (s), 157.2 (s), 149.2 (s), 137.3 (d), 134.2 (s), 131.9 (d), 129.0 (d, 2C), 129.0 (d, 2C), 127.5 (d, 2C), 126.3 (s), 125.8 (d, 2C), 35.2 (s), 31.1 (q) ppm; IR (ATR): ṽ 3124, 3067, 2968, 2958, 2904, 2866, 1925, 1635, 1607, 1552, 1522, 1470, 1446, 1405, 1359, 1318, 1302, 1268, 1245, 1161, 1108, 1070, 1024, 996, 946, 901, 891, 841, 781, 770, 720, 709, 682, 624; HRMS (ESI) Calcd for $[C_{20}H_{19}NO_2]$ ($[M+H]^+$) 306.1494, found 306.1483.

(2-Methoxyphenyl)(2-phenyloxazol-5-yl)methanone (**3c**)

Yield 70%, yellow solid, m.p. 134-135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 - 8.16 (d, J = 8.0 Hz, 2H), 7.67 (s, 1H), 7.54-7.48 (dt, J = 11.3, 7.2 Hz, 5H), 7.08-7.03 (m, 2H), 3.83 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.7 (s), 164.6 (s), 157.6 (s), 149.9 (s), 137.9 (d), 133.0 (d), 131.9 (d), 129.8 (d, 2C), 129.0 (d), 127.5 (d, 2C), 127.4 (s), 126.3 (s), 120.6 (d), 111.7 (s), 55.7(q) ppm. IR (ATR): ṽ 2962, 2925, 2853, 2836, 1654, 1599, 1580, 1563, 1527, 1491, 1449, 1361, 1284, 1255, 1159, 1096, 1047, 1022, 993, 946, 922, 900, 802, 783, 764, 714, 685, 665, 614 ; HRMS (ESI) Calcd for $[C_{17}H_{13}NO_3]$ ($[M+H]^+$), 280.0973, found 280.0968.

(3-Methoxyphenyl)(2-phenyloxazol-5-yl)methanone (**3d**)

Yield 72%, white solid, m.p. 95-96 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21-8.20 (m, J = 7.8 Hz, 2H), 7.88 (s, 1H), 7.60-7.58 (d, J = 7.7 Hz, 1H), 7.55-7.50 (m, 4H), 7.47-7.44 (t, 1H), 7.20-7.18 (m, J = 10.2 Hz, 1H), 3.89 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.2 (s), 164.8 (s), 159.9 (s), 149.0 (s), 138.2 (s), 137.8 (d), 132.0 (d), 129.8 (d),129.0 (d, 2C), 127.5 (d, 2C), 126.2 (s), 121.5 (d), 119.7 (d), 113.4 (d), 55.5 (q) ppm; IR (ATR): ṽ 3126, 3078, 3003, 2836, 1645, 1557, 1524, 1478, 1446, 1425, 1357, 1302, 1254, 1151, 1080, 1040, 1013, 995, 957, 918, 895, 860, 803, 793, 777, 748, 711, 684; HRMS (ESI) Calcd for $[C_{17}H_{13}NO_3]$ ($[M+H]^+$), 280.0973, found 280.0968.

(4-Methoxyphenyl)(2-phenyloxazol-5-yl)methanone (**3e**)

Yield 75%, white solid, m.p. 135-136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20-8.18 (d, J = 8.2 Hz, 2H), 8.06-8.04 (d, J = 8.9 Hz, 2H), 7.87 (s, 1H), 7.56-7.50 (t, J = 7.7 Hz, 3H), 7.04-7.02 (d, J = 8.9 Hz, 2H), 3.91 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0 (s), 164.4 (s), 163.8 (s), 149.2 (s), 136.8 (d), 131.8 (d, 2C), 131.5 (d), 129.5 (s), 129.0 (d), 127.4 (d), 126.4 (s), 114.1 (d), 55.6 (q) ppm; IR (ATR): ṽ 3128, 3033, 2959, 2846, 1653, 1601, 1559, 1525, 1511, 1473, 1453, 1360, 1323, 1263, 1246, 1163, 1116, 1073, 1024, 992, 947, 901, 840, 795, 783, 761, 719, 707, 692, 636, 624; HRMS (ESI) Calcd for $[C_{17}H_{13}NO_3]$ ($[M+H]^+$) 280.0973, found 280.0968.

(4-Fluorophenyl)(2-phenyloxazol-5-yl)methanone (**3f**)

Yield 71 %, white solid, m.p. 153-154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13-8.11 (m, 2H), 8.01-7.98 (m, 2H), 7.82 (s, 1H), 7.50-7.43 (dq, 3H), 7.19-7.15 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8 (s), 166.9 (s), 164.8 (s), 164.8 (s), 148.9 (s), 137.6 (d), 133.1 (s), 132.0 (d), 131.7 (d), 131.6 (d), 129.0 (d, 2C), 127.5 (d, 2C), 126.2 (d), 116.1 (d), 116.0 (d) ppm; IR (ATR): ṽ 3129, 3077, 3055, 1925, 1746, 1651, 1600, 1558, 1526, 1507, 1478, 1449, 1409, 1359, 1319, 1290, 1233, 1175, 1159, 1103, 1073, 1016, 995, 947, 922, 899, 853, 813, 780, 758, 715, 702, 685, 639, 621; HRMS (ESI) Calcd for $[C_{16}H_{10}FNO_2]$ ($[M+H]^+$), 268.0774, found 268.0764.

(3,5-Dichlorophenyl)(2-phenyloxazol-5-yl)methanone (**3g**)

Yield 73%, white solid, m.p. 80-81 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19-8.18 (d, J = 6.9 Hz, 2H), 7.93 (s, 1H), 7.87 (d, J = 1.9 Hz, 2H), 7.63-7.62 (t, J = 1.9 Hz, 1H), 7.59-7.51 (dt, J = 14.4, 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4 (s), 165.4 (s), 148.3 (s), 139.1 (s), 138.5 (d), 135.8 (s), 132.9 (d), 132.3 (d), 129.1 (d, 2C), 127.6 (d, 2C), 127.4 (d, 2C), 125.9 (s) ppm; IR (ATR): ṽ 3133, 3076, 1647, 1605, 1556, 1523, 1473, 1448, 1418, 1393, 1356, 1293, 1238, 1186, 1144, 1101, 1071, 1017, 999, 953, 933, 870, 806, 780, 750, 712, 684, 619; HRMS (ESI) Calcd for $[C_{16}H_9Cl_2NO_2]$ ($[M+H]^+$) 318.0088, found 318.0078.

(4-Bromophenyl)(2-phenyloxazol-5-yl)methanone (**3h**)

Yield 67%, white solid, m.p. 152-153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 -8.17 (d, J = 7.1 Hz, 2H), 7.89-7.88 (m, 3H), 7.70-7.68 (d, J = 8.4 Hz, 2H), 7.57-7.50 (dq, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2 (s), 164.9 (s), 148.8 (s), 137.8 (d), 135.5 (s), 132.1 (d,)2C, 130.5 (d, 2C), 129.1 (d, 2C), 128.5 (s), 127.5 (d, 2C), 126.1 (s) ppm; IR (ATR): ṽ 3135, 3062, 1921,1737, 1638, 1585, 1550, 1472, 1448, 1395, 1360, 1322, 1309, 1247, 1169, 1011, 995, 946, 927, 898, 836, 780, 753, 717, 688, 618; HRMS (ESI) Calcd for $[C_{16}H_{10}BrNO_2]$ ($[M+H]^+$), 327.9973, found 327.9965.

Acknowledgements

Y.X is grateful to the National Natural Science Foundation of China (no. 21808246) and Jiangsu Overseas Visiting Scholar Program for University Prominent Young & Middle-aged Teachers and Presidents; Q. W is grateful to the CSC (China Scholarship Council) for a Ph.D. fellowship, Z. Z. for a Ph.D. fellowship from the Guangzhou Elites Scholarship Council.

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10.1002/adsc.201801386

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