Ligand Design

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Optimizing P,N-Bidentate Ligands for Oxidative Gold Catalysis: Efficient Intermolecular Trapping of α-Oxo Gold Carbenes by Carboxylic Acids**

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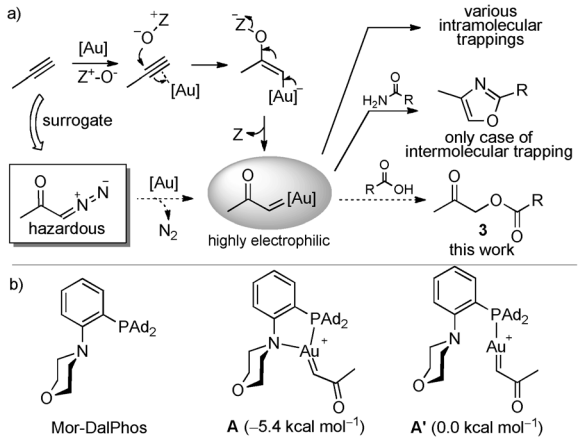
A few years ago we reported[1] that gold-catalyzed[2] intermolecular oxidation of alkynes offered an expedient access to synthetically versatile α-oxo gold carbene intermediates (Scheme 1 a). This strategy circumvents the use of hazardous and potentially explosive α-diazo ketone precursors[3] and has led to the development of various efficient synthetic methods, by us[1,4] and others,[5] based on intramolecular trapping of α-oxo gold carbene intermediates. The intermolecular counterpart, which is likely to be of exceptional synthetic utility, however, proves to be very challenging because of the highly electrophilic nature of the carbene center and is often plagued with overoxidation, reactions with solvents,[4b,g] and intractable side reactions. Earlier we reported for the first time that the reactivity of the gold carbene could be attenuated by using bidentate phosphine ligands so that it reacted with carboxamides efficiently, thus leading to a one-step synthesis of 2,4-disubstituted oxazoles.[6] Mor-DalPhos (see Scheme 1 b),[7] a bulky P,N-bidentate ligand, was found to be a uniquely effective ligand, and its role was proposed to enable the formation of a tricoordinated gold carbene (e.g., **A**) instead of the typical dicoordinated one (e.g., **A′**). The tricoordination leads to attenuated electrophilicity at the carbene center (Scheme 1 b).



Scheme 1. a) Trapping α-oxo gold carbenes generated by intermolecular alkyne oxidation using internal and external nucleophiles. b) Mor-DalPhos and the previously calculated relative energies (kcal mol^{-1}) of the corresponding gold carbene species. The PBE1PBE/6-311 + G** level of theory was used.[6]

To further develop alkynes as surrogates of hazardous α-diazo ketones in gold catalysis, especially in the context of synthetically important intermolecular trapping, we embarked on expanding the scope of suitable external nucleophiles beyond carboxamide. Our first target was carboxylic acids (Scheme 1 a), a weaker nucleophile in its neutral form than carboxamide. Notably, the reaction, if developed, would offer a novel and rapid access to synthetically versatile α-carboxymethyl ketones (**3**; Scheme 1 a) from readily available terminal alkynes and carboxylic acids.

At the outset, we used 1-dodecyne and benzoic acid (1.2 equiv) as the reacting partners and 8-methylquinoline *N*-oxide[4d] as the oxidant, and the results of reaction optimization are shown in Table 1. Consistent with our previous study,[6] cationic gold complexes derived from typical ligands such as Ph_3P, IPr, and BrettPhos (Figure 1 a) were largely ineffective, thus resulting in complex mixtures with little desired product (entry 1). On the contrary, Mor-DalPhos[7] again proved to be an effective ligand, and the oxidative gold catalysis led to the desired α-benzoxymethyl ketone **3a** in a fairly good yield (entry 3). An identical yield was observed with the ligand **L1**,[7] which differs from Mor-DalPhos by having a piperidine ring instead of a morpholine ring (entry 4). However, the smaller Me-DalPhos[7] was inferior (entry 2), thus suggesting that the steric size of the pendant secondary amine might be critical.

Consequently, we modified the piperidine ring of **L1** with different substituents. While the installation of a methyl group at its 4-position was inconsequential (Table 1, entry 5; see **L2** in Figure 1 b), the much bigger *tert*-butyl group was detrimental (entry 6). However, to our delight, a 3-methyl group, as in **L4**, led to a notable increase of the reaction yield (entry 7). Moreover, the use of *cis*-3,5-dimethylpiperidine (**L5**) as the pendant amine group resulted in a higher 84% yield of **3a** (entry 8). On the contrary, **L6** with a *trans*-3,5-dimethylpiperidine ring led to a much less efficient reaction (entry 9), which could be attributed to deleterious steric congestion caused by an inevitable axially oriented methyl group. The piperidine ring in **L5** could be replaced with a morpholine ring (**L7**) with only a small, yet adverse impact

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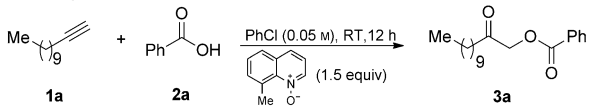
Table 1: Optimization of the reaction conditions.[a]



Entry	**1a**/**2a**	Catalyst	Yield [%][b]
1	1:1.2	[**L**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)	< 7[c]
2	1:1.2	[(Me-DalPhos)AuCl](5 mol%)/ $NaBAr^F_4$(10 mol%)	11
3	1:1.2	[(Mor-DalPhos)AuCl](5 mol%)/ $NaBAr^F_4$(10 mol%)	68
4	1:1.2	[**L1**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)	68
5	1:1.2	[**L2**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)	68
6	1:1.2	[**L3**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)	18
7	1:1.2	[**L4**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)	75
8	1:1.2	[**L5**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)	84
9	1:1.2	[**L6**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)	30
10	1:1.2	[**L7**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)	79
11	1:1.2	[**L8**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)	63
12	1.3:1	[**L7**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)	86
13	1.3:1	[**L5**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)	98[d]
14	1.3:1	[**L5**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)[e]	95
15	1.3:1	[**L5**AuCl](5 mol%)/$NaBAr^F_4$(10 mol%)[f]	88

[a] The reaction was run with everything except the oxidant in a vial capped with a septum, and the oxidant was introduced into the reaction mixture over a 12 h period using a syringe pump. Initially, [**1a**] = 0.1 M. [b] Measured by ^{1}H NMR analysis using diethyl phthalate as the internal standard. [c] **L** = Ph_3P, IPr, or BrettPhos. The ^{1}H NMR spectra of the crude reaction mixture were mostly messy. [d] Yield of isolated product was 96%. [e] DCE was used as the solvent. [f] Toluene was used as the solvent.

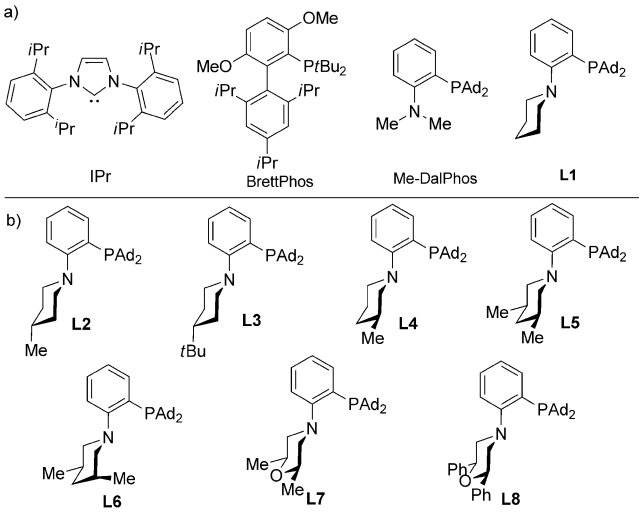


Figure 1. a) known ligands. b) Newly developed P,N-bidentate ligands. Ad = adamantyl.

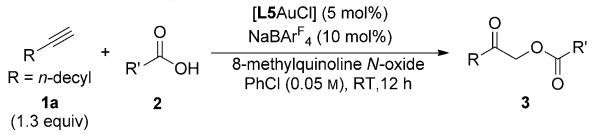
on the reaction outcome (entry 10). Interestingly, replacing the methyl groups in **L7** with bigger phenyl groups (**L8**) resulted in a yield even lower than that obtained with by Mor-DalPhos (entry 11). This result, along with that of **L3**, suggest that there is an optimal steric bulk for the pendant six-membered ring in this reaction. When benzoic acid was the limiting reagent, **L5** was a significantly better ligand than **L7** for the gold catalysis (compare entries 12 and 13). Moreover, the reaction yield in the former case is nearly quantitative, which is impressive considering the difficulties previously encountered in trapping these reactive gold carbene species and really showcased the opportunities in method development based on ligand design/development. Other solvents such as DCE (entry 14) and toluene (entry 15) were suitable for this reaction, albeit not nearly as good as PhCl. Although the oxidant, 8-methylquinoline *N*-oxide, had to be introduced to the reaction slowly by a syringe pump to avoid over oxidation, the reaction proceeded smoothly at ambient temperature.

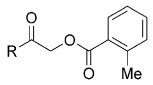
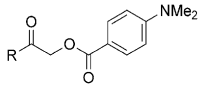
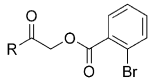
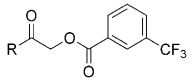
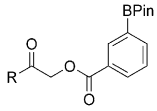
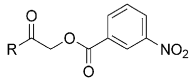
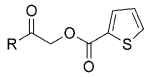
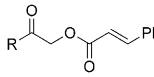
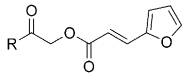
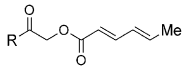
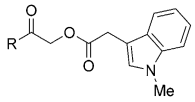
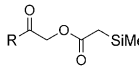
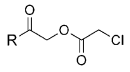
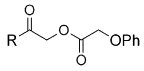
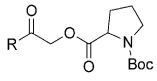
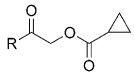
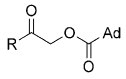
With the optimized reaction conditions given in Table 1, entry 13, the scope of the transformation was first examined with various carboxylic acids. As shown in Table 2 (entries 1–6), various substituted benzoic acids reacted smoothly, affording the desired products in mostly excellent yields. Even a Bpin group was tolerated, and the relatively low yield was due to the coelution of the boronated product **3f** with 8-methylquinoline (entry 5). The reaction also worked well with other conjugated acids such as thiophene-2-carboxylic acid (entry 7), *trans*-cinnamic acid (entry 8), *trans*-3-(2-furyl)-acrylic acid (entry 9), and *trans, trans*-hexa-2,4-dienoic acid (entry 10), thus delivering the corresponding products in greater than 90% yields. Acetic acids with the α-carbon atom functionalized by a 1-methylindol-3-yl (entry 11), trimethylsilyl (entry 12), chloro (entry 13), and phenoxy group (entry 14), were all suitable substrates, and functionalized α-carboxymethyl ketones were again isolated in good to excellent yields. The reaction with N-Boc-protected proline, however, only resulted in a serviceable yield of the corresponding product (entry 15). Other carboxylic acids such as cyclopropanecarboxylic acid (entry 16) and adamantane-1-carboxyclic acid (entry 17) also proceeded well. While these reactions were run on a 0.2 mmol scale, a 3 mmol scale was readily implemented with the reaction in entry 2 even with only 2 mol% of the catalyst and **3c** was isolated in 82% yield.

The reaction also proceeded smoothly with various terminal alkynes. As shown in Table 3, phenylacetylene (entry 1) and 1-ethynylcyclohexene (entry 4) were excellent substrates, and so are the acetylenes substituted by cyclic (entries 2 and 3) or remotely functionalized linear alkyl groups (entries 5–7). The reaction yields were good to excellent. Even with heteroatoms placed close to the C–C triple bond and hence to the in situ formed electrophilic gold carbene center, this intramolecular reaction still led to a good (entry 8) or serviceable yield (entry 9).

The ligand optimization by modification of the pendant piperidine/morpholine ring deserves further examination. In our previous carboxamide trapping chemistry,[6] the smaller Me-DalPhos was found to be equally effective as a bidentate ligand such as Mor-DalPhos. On the contrary, in this chemistry, the steric size of the pendant amino group is crucial for the reaction outcome (see Table 1). We attribute the difference to the decreased nucleophilicity of the carbonyl oxygen group in the carboxylic acid[8] as compared to that in the carboxamide. It is reasonable to suspect that steric shielding around the gold carbene center would facilitate, to

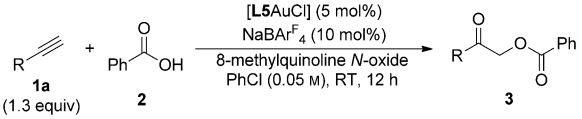
Table 2: Reaction scope with different carboxylic acids.[a,b]

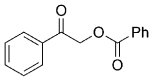
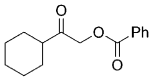
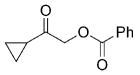
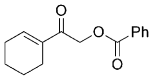
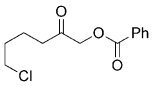
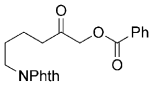
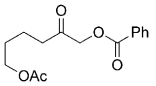
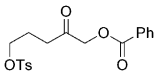
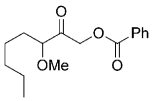


Entry	Product		Yield [%]
1		**3b**	94
2		**3c**	96
3		**3d**	91
4		**3e**	92
5		**3f**	66 (85[c])
6		**3g**	68
7		**3h**	90
8		**3i**	94
9		**3j**	97
10		**3k**	93
11		**3l**	90
12		**3m**	92
13		**3n**	80
14		**3o**	78
15		**3p**	54
16		**3q**	91
17		**3r**	80

[a] Initially [**2**] = 0.1 M; the oxidant was introduced to the reaction vial over a 12 h period using a syringe pump. [b] Yields of isolated products are shown. [c] Yield determined by NMR spectroscopy. Boc = *tert*-butoxycarbonyl, Pin = pinacolato.

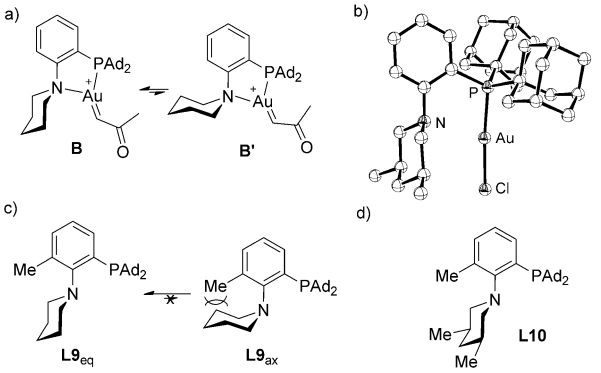
Table 3: Reaction scope with various alkynes.[a,b]



Entry	Product		Yield [%]
1		**3s**	93
2		**3t**	92
3		**3u**	95
4		**3v**	94
5		**3w**	90
6		**3x**	90
7		**3y**	92
8		**3z**	76 (85[c])
9		**3aa**	59

[a] Initially [**2**] = 0.1 M. The oxidant was introduced to the reaction vial using a syringe pump. [b] Yields of isolated products are shown. [c] Yield determined by NMR spectroscopy. Phth = phthaloyl, Ts = 4-toluenesulfonyl.

a certain extent, slower reactions with small nucleophiles by minimizing side reactions with sterically demanding nucleophiles. With regard to the ligands **L1** and Mor-DalPhos, the enhanced efficiency with **L5** could be attributed a priori to the bulkier piperidine ring. However, two *cis* methyl groups could at the same time impose conformation rigidity to the N-heterocycle. Scheme 2a outlines two chair conformers of the gold carbene intermediate with **L1** as its ligand. It is noteworthy that the X-ray diffraction studies of Mor-DalPhos palladium complexes by Stradiotto and co-workers[7a] reveal that the morpholine ring can adopt the chair conformation as shown in **B′** and twist boat conformations. The conformer **B′**, though understandably less stable and hence less populated, does not provide sufficient steric protection to the carbene center. Consequently, the reaction could be improved if the conformers including **B′** and other less shielding ones could be minimized. We surmise that the two *cis* methyl groups in **L5** might play the role of locking the piperidine into a conformation identical to that in **B**. As such, the carbene center is constantly shielded and hence would react preferably with smaller nucleophiles, such as carboxylic acids, rather than

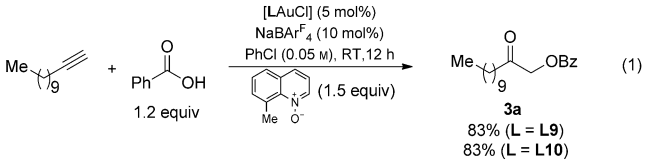


Scheme 2. a) Two chair conformers of the tricoordinated gold carbene with **L1** as the bidentate ligand. b) ORTEP drawing of [**L5**AuCl] with the solvent molecules omitted.[11] The thermal ellipsoids are shown at 50% probability. c) **L9** in two different chair conformers. d) The structure of **L10**.

bigger ones, including the oxidant. An X-ray diffraction study of [**L5**AuCl][11] confirmed the preferred shielding chair conformation for the *cis*-3,5-dimethylpiperidine ring (Scheme 2b). In the case of **L8**, the phenyl groups are likely too bulky to hinder the carbene formation or the productive approach by a carboxylic acid.

To offer more insight into the importance of conformation control, we prepared the ligand **L9** (Scheme 2c), wherein an *ortho*-methyl group on the benzene ring is installed to essentially prohibit the piperidine ring from adopting the chair conformation shown as $\mathbf{L9}_{ax}$ and likely minimizes the contribution of other nonchair conformers. Indeed, the gold catalyst afforded **3a** in 83% yield [Eq. (1)], which is much better than that obtained with **L1** (where the *ortho*-Me is absent) and virtually identical to that obtained by **L5** (see Table 1, entry 8). When **L10**, with an *ortho*-methyl group and a pendant *cis*-3,5-dimethylpiperidine was used for the gold catalysis, the reaction efficiency remained the same [Eq. (1)], thus suggesting that the role of the piperidine methyl groups in **L5** is to fix the desired chair conformation of the N-heterocycle instead of providing additional steric bulk.

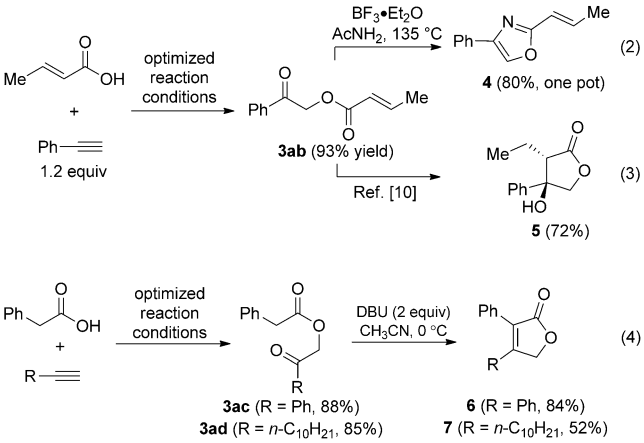
This one-step, generally applicable, and efficient synthesis of functionalized carboxylmethyl ketones permits rapid access to various useful cyclic structures. For example, the 2-



(1)

alkenyloxazole **4** was isolated in 80% yield by the combination of the gold catalysis and a subsequent $BF_3{\cdot}Et_2O$-promoted condensation[9] in a one-pot process [Eq. (2)]. Moreover, the phenone intermediate **3ab**, isolated in 93% yield, has been previously converted into the γ-lactone **5** in 72% yield [Eq. (3)].[10] Another approach to cyclized products is shown in Equation (4), where DBU effectively promoted sequential intramolecular aldol reaction and dehydration of the ketones **3ac** and **3ad**, which in turn were obtained in excellent yields by the oxidative gold catalysis.

In conclusion, we have developed a highly efficient and broadly applicable synthesis of carboxymethyl ketones from



readily available carboxylic acids and terminal alkynes under exceptionally mild reaction conditions. In this oxidative gold catalysis, the highly electrophilic α-oxo gold carbene intermediate is most likely generated, and its challenging intermolecular trapping by weakly nucleophilic carboxylic acids is achieved upon extensive optimization of the P,N-bidentate ligands coordinated to the gold center. While the steric bulk of the pendant amino group in these ligands is beneficial to a certain extent, controlling the conformation of the sterically suitable piperidine ring to provide better shielding to the carbene center appeared to be important to achieve the high efficiency. Importantly, the reaction products can be rapidly converted into synthetically versatile cyclic structures. Further studies employing other types of nucleophiles including so-far unyielding enol ethers are currently underway.

Experimental Section

General procedure for gold-catalyzed synthesis of α-carboxymethyl ketones: The carboxylic acid (0.2 mmol), alkyne (0.26 mmol), [**L5**AuCl] (0.01 mmol), and $NaBAr^F_4$ (0.02 mmol) were added sequentially to a 3 dram vial containing 2 mL of chlorobenzene. The resulting mixture was stirred at room temperature. To this vial a solution of *N*-oxide (47.7 mg, 0.3 mmol) in 4 mL of chlorobenzene was then added using a syringe pump over a 12 h period. Upon completion, the reaction mixture was concentrated under vacuum. The residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired product **3**.

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[8] ^{1}H NMR studies of a mixture of benzoic acid and 8-methylquinoline in [D_8]toluene confirmed that the benzoic acid is not deprotonated in the nonpolar solvent. As PhCl is also a nonpolar solvent, the acid should similarly stay in its neutral form in PhCl. Hence, it is most likely that the gold carbene intermediate are trapped by the neutral carboxylic acid in this reaction.

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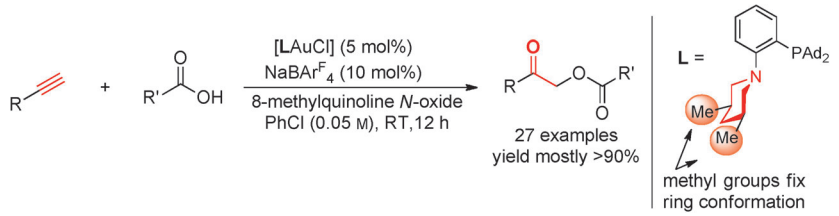
[11] CCDC 933214 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Communications

Ligand Design

K. Ji, Y. Zhao, L. Zhang* ___ ▮▮▮▮–▮▮▮▮

Optimizing P,N-Bidentate Ligands for Oxidative Gold Catalysis: Efficient Intermolecular Trapping of α-Oxo Gold Carbenes by Carboxylic Acids



Control confirmed: Optimization of P,N-bidentate ligands (**L**) reveals the importance of conformation control for intermolecular trapping of reactive α-oxo gold carbene intermediates. As a result, the highly efficient and broadly applicable synthesis of carboxymethyl ketones from readily available carboxylic acids and terminal alkynes proceeds under mild reaction conditions.