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An Industrial Perspective on Counter Anions in Gold Catalysis: Underestimated with Respect to "Ligand Effects"

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Abstract

The conversion of a variety of well-known test reactions, representing the key reactivity patterns of gold catalysis, were analyzed by GC and ^{1}H NMR. The study is focused on establishing of a strategical approach for the consideration of ligand influence and counter anion influence during the catalyst optimization including an industrial perspective. The study shows a dominance of the counter anion, a dominance which up to now has been neglected in most of the routine screenings. In addition, a drastic substrate-dependency became obvious, even a marginal variation of the substrate already could strongly effect the catalytic activity and change the optimal counter anion or ligand. Based on the collected data a strategic concept for an efficient screening for a specific substrate is introduced, this concept can serve as an important guideline for catalyst optimization in homogeneous gold catalysis.

Keywords

Alkynes, allenes; catalyst optimization; counter anion; gold; ligand,

Introduction

Homogeneous gold catalysis evolved into a topic of considerable interest.[1] The centerpiece in each gold-catalyzed reaction is the gold catalyst. Cationic gold species

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are considered to be the most effective catalysts in the electrophilic activation of alkynes for the addition of a diversity of nucleophiles. However, in the literature the choice of the gold catalyst often seems to be random and so far the strategic approach to the optimization with respect to the ligand and counter anion of the catalyst is inadequate, if involved at all.[2] This becomes obvious by an analysis of publications concerning the most recent experimental studies in gold catalysis published in 2017 (Figure 1: 116 publications at 16.11.2017, Scifinder, keyword: gold catalyzed; only experimental studies are included). Mainly the ligand system of the gold(I) catalyst was examined, 31 % of all incorporated publications only deal with ligand variations. 32 % are based on an initial variation of the ligand, followed by a variation of the counter anion for the most successful ligand. Thus, overall 63 % are first and foremost focusing on ligand variations during the catalyst optimization. In 4 % only the counter anion was varied, in 10 % after the screening of counter anions a ligand variation followed. Although counter anion effects are well described in literature,[3] the choice of counter anion is still empirical and its role in screenings is mostly neglected. 17 % of the reports only vary other parameters like substrate concentration, solvent or temperature. In a few reports (6 %) the catalyst screening is performed without any recognizable pattern. Overall, the average number of screened ligands is as low as 4.2 per publication, the average number of applied counter anions is only 2.1. Interestingly, in almost one half of the reports (31 % + 17 % = 48 %) the counter anion was not varied at all.

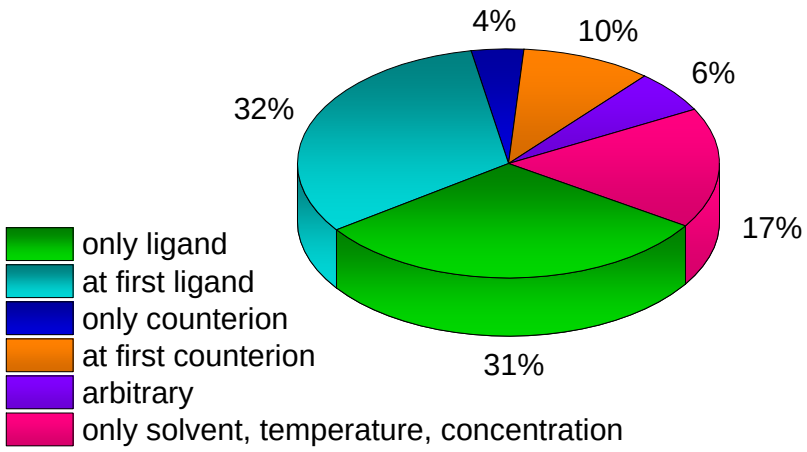

Figure 1. Overview of the applied catalyst optimization procedures in the year 2017.

This analysis shows that the effect of the ligand[4] is mostly expected to be more pronounced than counter anion influences in gold(I) catalysis.[5] Only in a few publications the latter is addressed at all, for example by Zuccaccia and co-workers

who examined the counter anion-impact in the gold(I)-catalyzed alkoxylation of alkynes by DFT calculations.[6] Thereby, they demonstrated an influence of the coordinating ability, basicity and geometry of the counter anion on all steps of the reaction mechanism. Furthermore, Hammond and co-workers introduced a method to predict the counter anion effect and the accompanying reactivity in cationic gold catalysis by a gold affinity index and a hydrogen bonding basicity index,[7] which mainly addresses the potential inhibition of the catalyst by the counter anion still coordinating. However, a general study for the development of an efficient procedure to identify the gold catalyst with the best catalytic activity, systematically involving both ligand and counter anion, is still missing and highly desirable from an industrial view on homogeneous gold catalysis. This encouraged us to shed light on the decisive factors for a strategical approach for the catalyst screening in the course of the reaction optimization. It should be noted that the ligand and counter anion effects are analyzed in this study, the reasons for the observed effects are not part of this analysis but of an ongoing, more extensive study.

Results and Discussion

As an entry point, the literature-known cyclopropanation of styrene by a propargyl pivalate was chosen as a test reaction.[8] One equivalent of pivalate ([2-methylbut-3-yn-2-yl pivalate] = 0.048 mmol/ml) was treated with four equivalents of freshly distilled styrene and 0.5 – 0.05 mol% gold(I) complex in DCM at 25 °C for 15 h using *n*-dodecane as internal standard (Scheme 1). We systematically varied ligand and counter anion combinations of the gold(I) catalyst and detected the impact on the catalytic activity. To exclude any “silver effects”[9] arising from *in situ* activation, we isolated and purified a set of 24 gold(I) complexes of the type L-Au-X using NHC, phosphine and phosphite ligands in combination with the three established counter anions X = NTf_2^-, SbF_6^- and BF_4^-. In a few exceptions, it was not possible to isolate the activated gold(I) complexes. In these cases, the silver salt was removed by filtration through Celite before the reaction was started. The achieved turnovers (TOs) were used to describe the catalyst efficiency and the stability of the catalytic system. As shown in Figure 2, a remarkable impact of the counter anion on the gold catalysis was observed.

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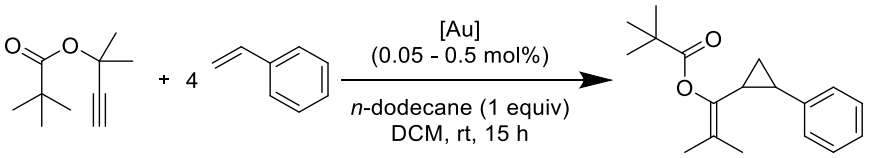

Scheme 1. Cyclopropanation of styrene with a propargyl pivalate.

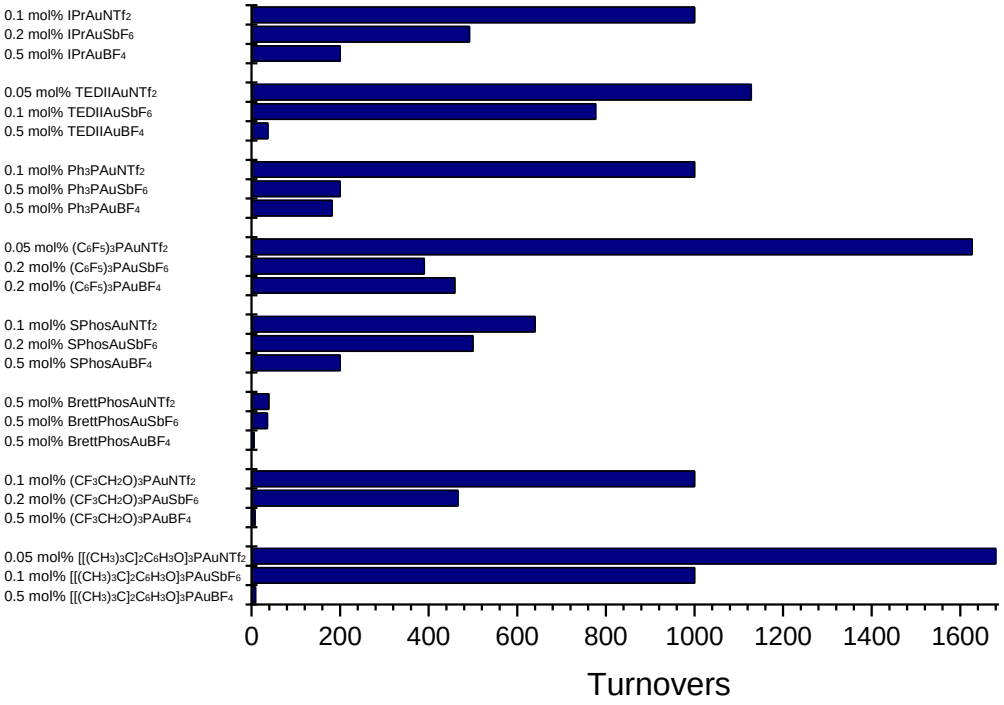

Figure 2. Catalytic activity of selected gold(I) complexes.

Interestingly, for almost all tested ligands the reactivity order concerning the counter anions was equivalent. In the case of BF_4^-, the catalytic reaction often was even inhibited. Using the counter anion NTf_2^- in combination with various ligands always led to the best result. Whereas, the counter anion SbF_6^- for almost every ligand has taken second place in the examined ranking. *Due to this result, it is not requisite to examine the counter anions for each ligand, which is a tremendous simplification of the overall screening procedure.* The influence of the ligand was less pronounced, with the exception of the bulky BrettPhos ligand which exhibited a drastic decrease of the TOs.

Based on these results, now a stronger focus was put on the role of the counter anion in the subsequent experiments. A variety of counter anions, namely Cl^-, NTf_2^-, OTf^-, SbF_6^-, BF_4^- and OTs^- were selected. As ligands we choose an NHC, a phosphine and a Buchwald ligand (namely IPr, PPh_3 and SPhos) in combination with the mentioned counter anions. *As soon as the counter anion with the highest catalytic activity was identified, a further optimization cycle was conducted with a larger pool of ligands*

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(Scheme 2). In Figure 3, a direct comparison of the common catalyst screening and our simplified screening method divided into **Screening A** and **Screening B** is visualized. In case of our investigated 22 ligands / 6 counter anions combination, a holistic catalyst screening of the full ligand/counter anion (22 x 6) matrix requires 132 test reactions. Whereas, a pre-screening (**Screening A**) to determine the best of the 6 counter anions with the 3 initial ligands, followed by a screening (**Screening B**) of the remaining 19 ligands in combination with the optimal counter anion from **Screening A**, leads to the best catalyst within 3 x 6 + 19 = 37 experiments. This simplification becomes possible as we observed the same trends with respect to the counter anions for each ligand (see Figure 2). Hence, it is possible to reduce the workload by 72 %. In principle, this amount of test reactions potentially could even be minimized by using just one active ligand in **Screening A**.

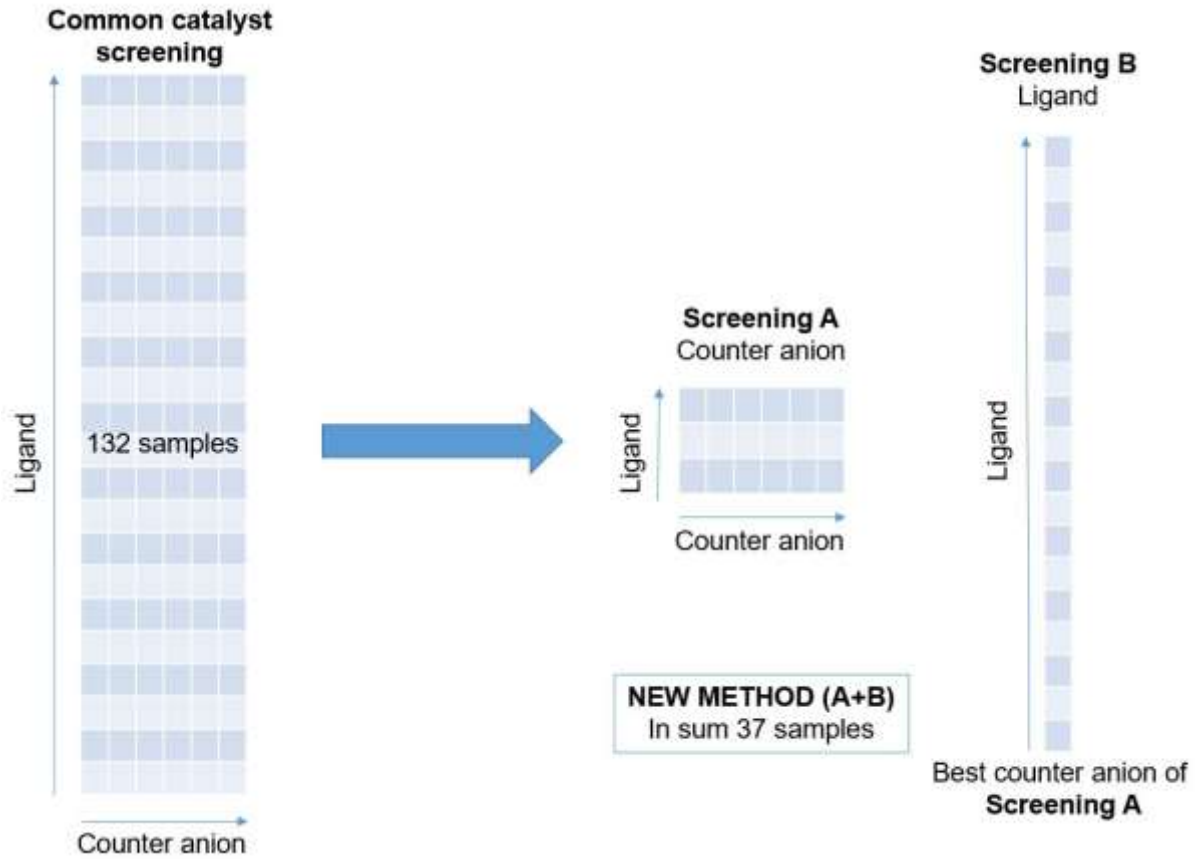

Figure 3. Simplified screening method.

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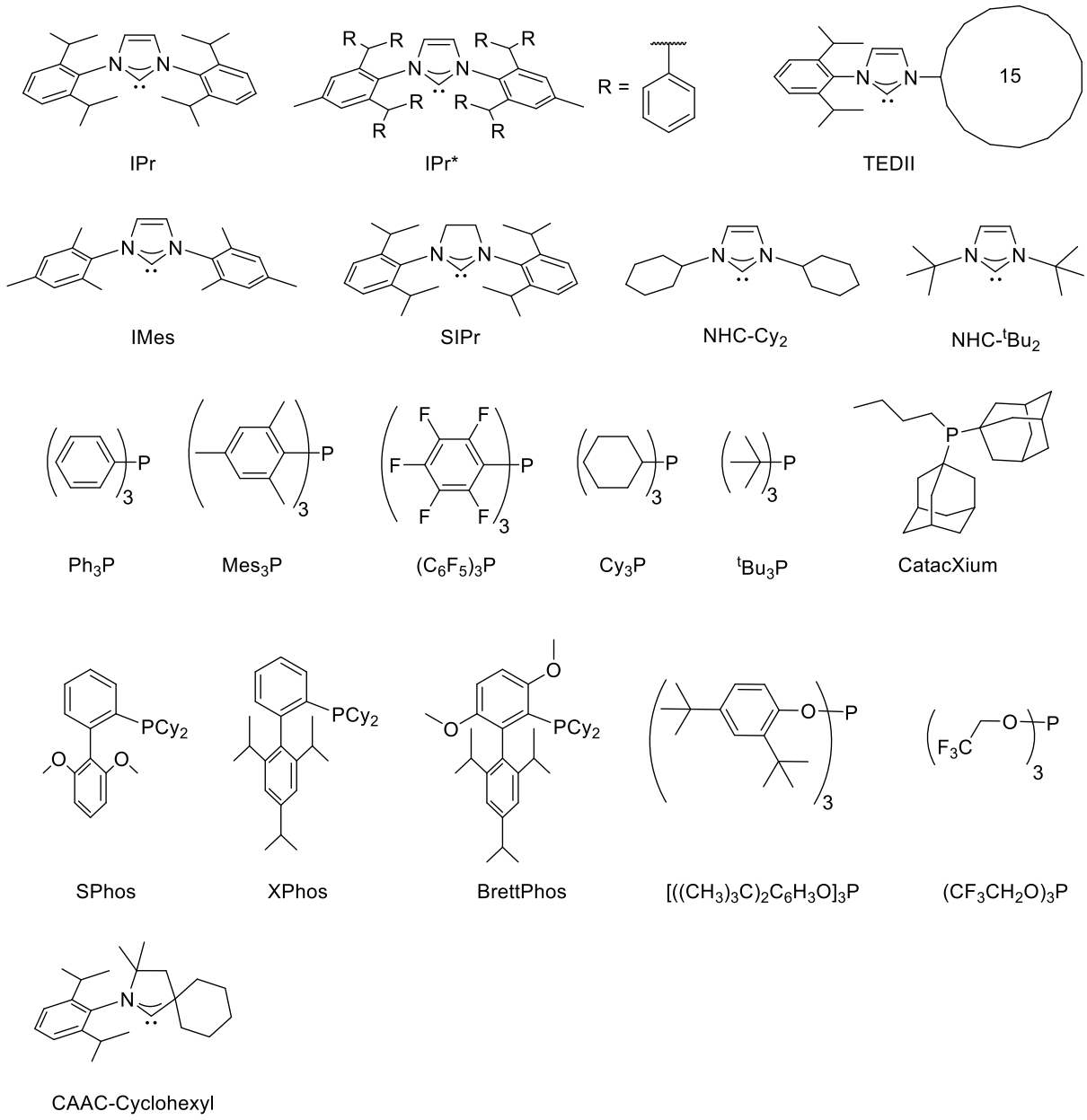
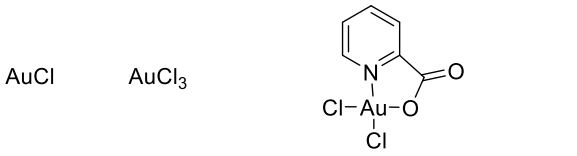
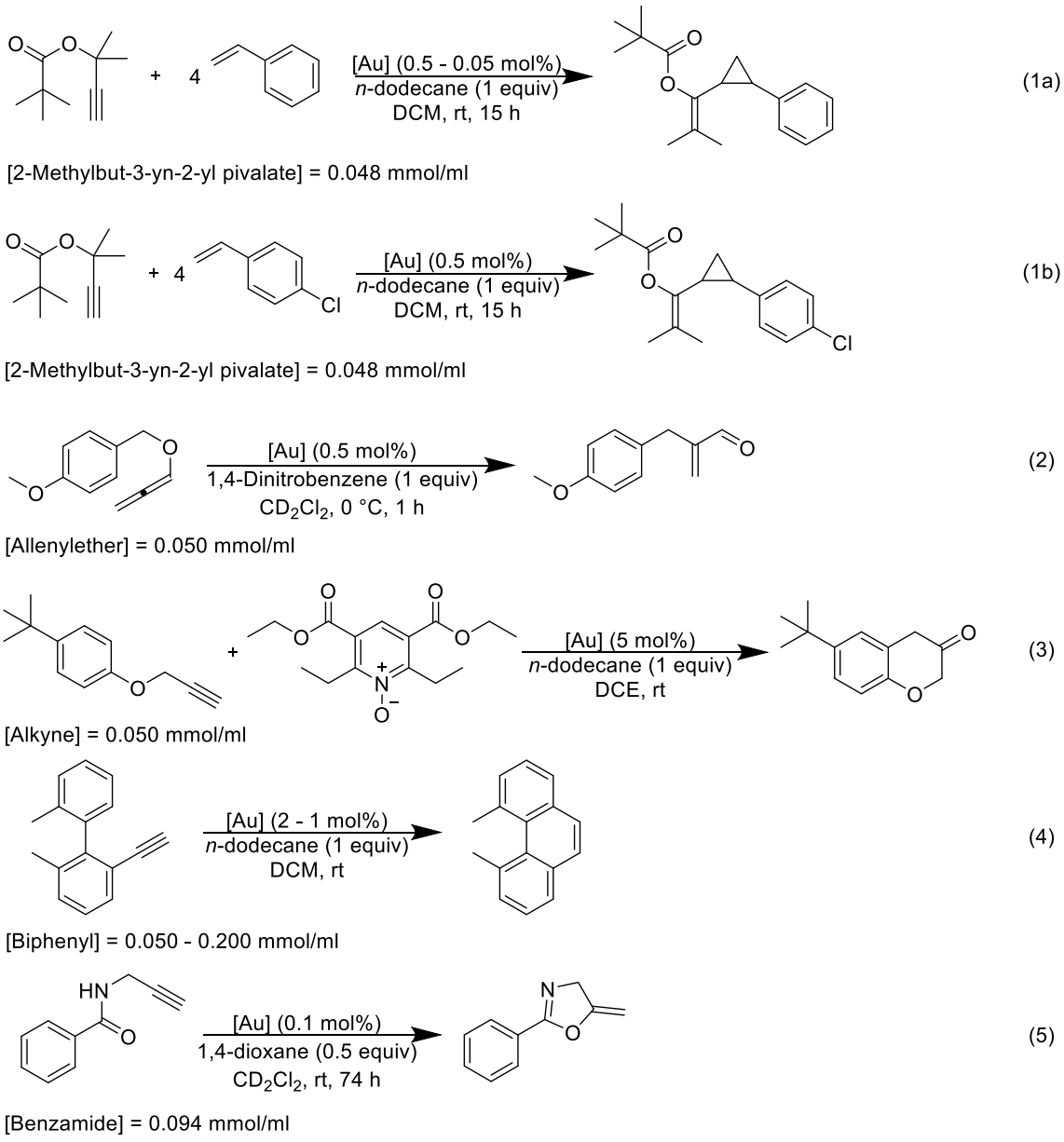




Scheme 2. Pool of ligands and complexes

To further support this approach, well-known and previously investigated reactions as representatives of main reactivity patterns in gold catalysis were chosen (Scheme 3):[8a,10] Cyclopropanation (Equations 1a and 1b) as a probe for a possible substrate dependence, the rearrangement of an allenylether (Equation 2), oxidative gold catalysis using *N*-oxides (Equation 3), a hydroarylation (Equation 4) and an

alkylideneoxazoline synthesis (Equation 5) as representative for the formation of a heterocycle were selected. All reactions were monitored by GC or ^{1}H NMR techniques which ensured an efficient analysis. Pre-screening of the reactions for reproduceable conditions, involving solvent, concentration, temperature and internal standard were conducted.



Scheme 3. Selected test reactions.

Cyclopropanation (Scheme 3, Equation 1a, 1b)

In the case of the cyclopropanation reaction a GC screening in DCM was conducted. If a complete consumption of the starting material was observed within a reaction time of 15 h a lower catalyst loading was used. Based on the new strategy, **Screening A**

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(Figure 4) was applied. The suitability of an optimized catalyst to reactions of the same reaction type but electronically different substrates was checked by the introduction a chloro substituent (Equation 1b).

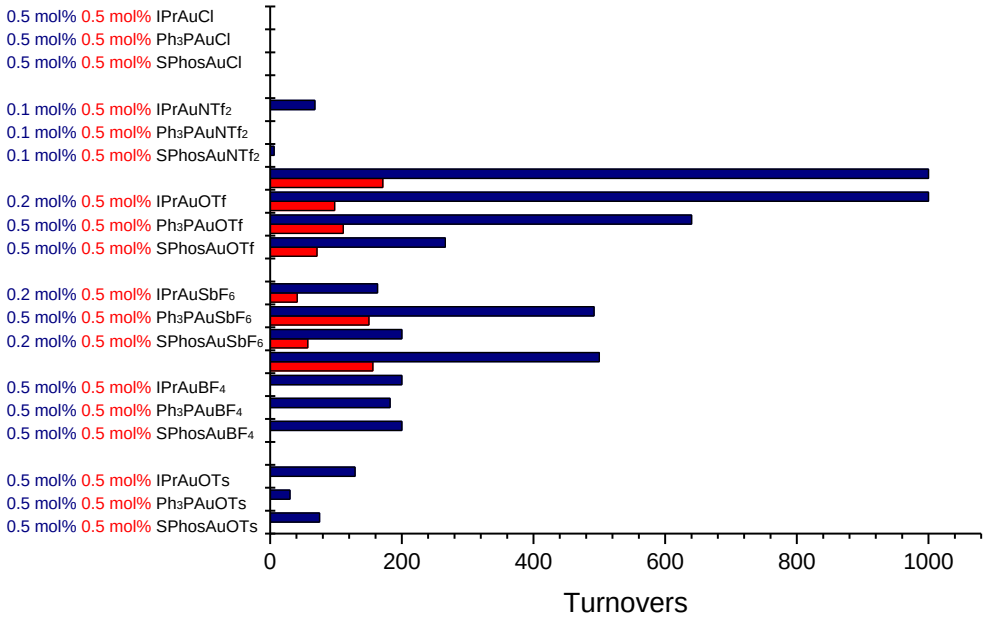

Figure 4. Counter anion effect with respect to the electronic nature of the substrate; (a, blue) cyclopropanation of styrene by a propargyl pivalate; (b, red) cyclopropanation of 4-chlorostyrene by a propargyl pivalate.

Figure 4 shows a significant counter anion influence. In both cases, the best result was observed with NTf_2^-. In comparison, the counter anions Cl^-, BF_4^- and OTs^- reached an activity which in some cases was up to 90 % lower. Furthermore, an immense substrate dependency was observed. In total, the catalyst performance for 4-chlorostyrene (Figure 4b) was slightly better for using NTf_2^- instead of SbF_6^- as counter anion. In comparison to Figure 4a, the choice of the counter anion for further examinations is not explicit. Moreover, the turnovers compared to the cyclopropanation with styrene (Figure 4a) are significantly reduced and in combination with the counter anions Cl^-, BF_4^- and OTs^- no conversion was detected. As a next step, various ligands were analyzed in combination with NTf_2^- as counter anion for both styrene derivatives (Figure 5).

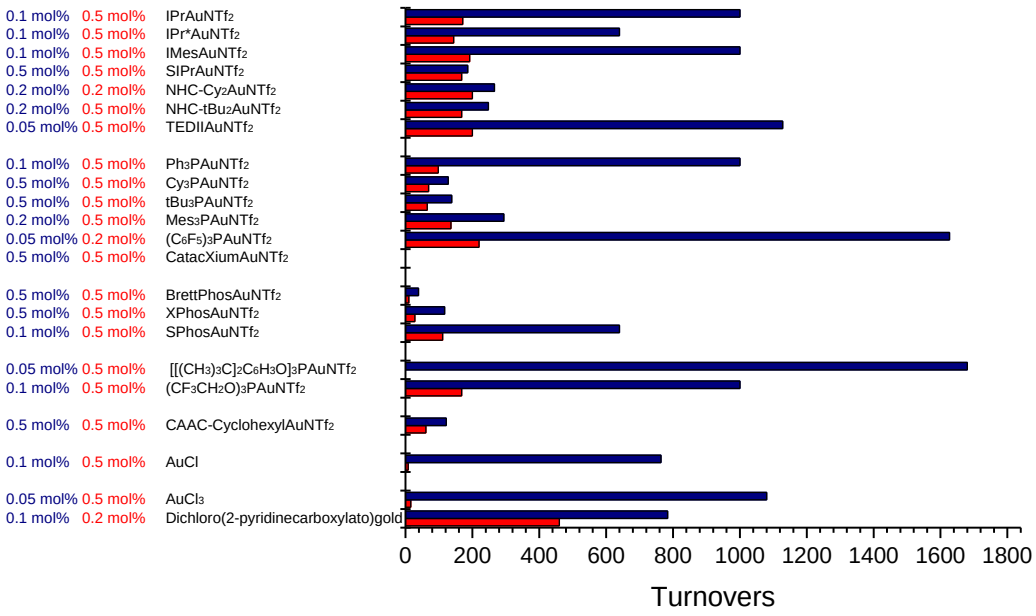

Figure 5. Direct comparison of the ligand influence concerning substrate dependency; (a, blue) cyclopropanation of styrene with a propargyl pivalate; (b, red) cyclopropanation of 4-chlorostyrene with a propargyl pivalate.

A strong substrate dependency within the same reaction type was also observed for this test. In case of styrene (Figure 5a), the $(C_6F_5)_3PAuNTf_2$ and $[((CH_3)_3C)_2C_6H_3O]_3PAuNTf_2$ catalysts achieved the best turnover numbers while for 4-chlorostyrene (Figure 5b) $AuCl_3$ showed the highest catalytic activity.

In case of styrene (Figure 5a), the $(C_6F_5)_3PAuNTf_2$ (TON = 1627) and $[((CH_3)_3C)_2C_6H_3O]_3PAuNTf_2$ (TON = 1680) catalysts achieved the best turnover numbers while for 4-chlorostyrene (Figure 5b) dichloro(2-pyridinecarboxylato)gold (TON = 460) showed the highest catalytic activity. In comparison, in the literature for the cyclopropanation of styrene with a pivalate the in situ activated gold(I) catalyst Ph_3PAuCl/ $AgSbF_6$ achieved only 15 turnovers.[8a] 100 turnovers were reported by Alcarazo and co-workers using a cyclopropenylylidene-stabilized dialkyl phosphenium cation as ligand.[8b] The corresponding conversion of 4-chlorostyrene has not been reported in the literature.

1,3 Rearrangement of an allenylether (Scheme 3, Equation 2)

On the GC columns available in the group, the starting material and product had the same retention time. Thus detection by gas chromatography was not possible and the

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reaction was monitored by ^{1}H NMR using 1,4-dinitrobenzene as internal standard (Figure 6). Within the examined test series, a limited selectivity of the reaction was monitored for all reactions in **Screening A**. Especially, the combination of the IPr ligand with different counter anions, with exception of SbF_6^-, exclusively led to hydrolysis[10a] of the allenylether. Within the three ligand systems, the counter anion SbF_6^- provided the best results with respect to the turnovers as well as the selectivity of the reaction. Due to this fact, further examinations concerning ligands were conducted with the counter anion SbF_6^- (Figure 7).

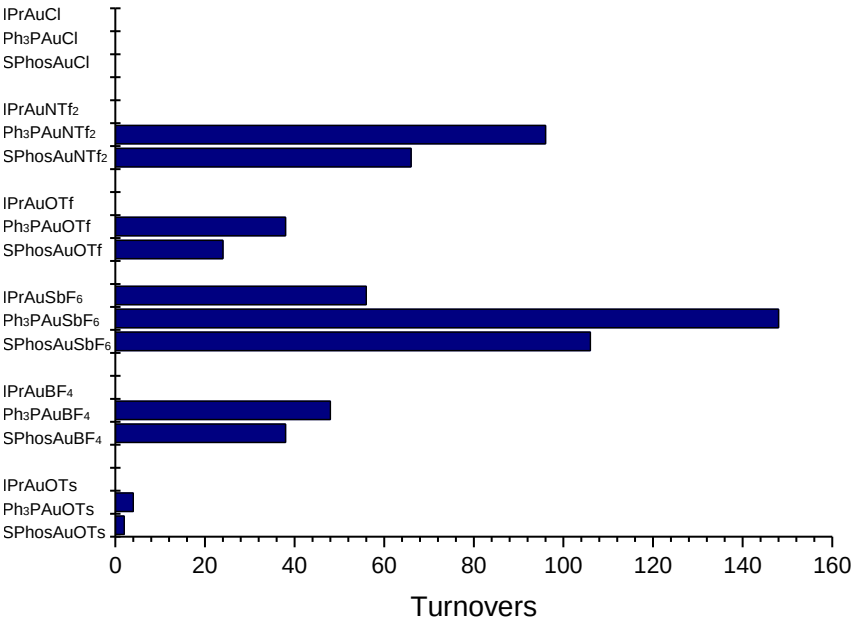

Figure 6. Counter anion effect on the 1,3 rearrangement of an allenylether.

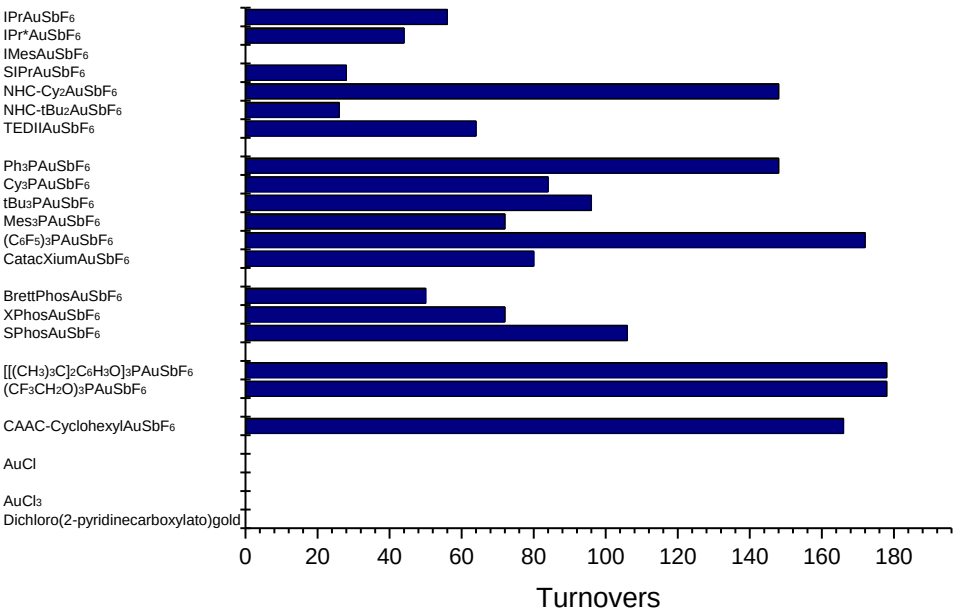

Figure 7. Ligand influence on the 1,3 rearrangement of an allenylether.

The best turnover numbers and selectivities were achieved with the investigated phosphite ligands, closely followed by the catalysts $(C_6F_5)_3PAuSbF_6$ and CAAC-Cyclohexyl-$AuSbF_6$. No reaction was observed by using AuCl or gold(III) complexes.

In the literature only hydrolysis was observed with this substrate, the authors used Ph_3PAuCl in combination with the silver salts $AgNTf_2$ and $AgSbF_6$ for this substrate.[10a] Our screening for the first time led to a catalyst that is able to induce the desired rearrangement.

Oxidative gold catalysis (Scheme 3, Equation 3)

Because of the extended reaction times, the reaction solution was analyzed after 15 h, 40 h, 7 d and 14 d by gas chromatography. Like in the other examples, the turnovers are depending on the counter anions (Figure 8). In case of the counter anions OTs^- and Cl^- no reaction was detected with any of the investigated ligands. The only exception of the reactivity order was observed in the case of SPhosAuOTf. For this ligand other counter anions all delivered either no reaction or poor selectivity. Because of the unselective reaction of $SPhosAuBF_4$ and the slightly decreased turnover of Ph_3PAuBF_4 in comparison to its NTf_2^- analogues, the counter anion NTf_2^- was chosen for further examinations (Figure 9).

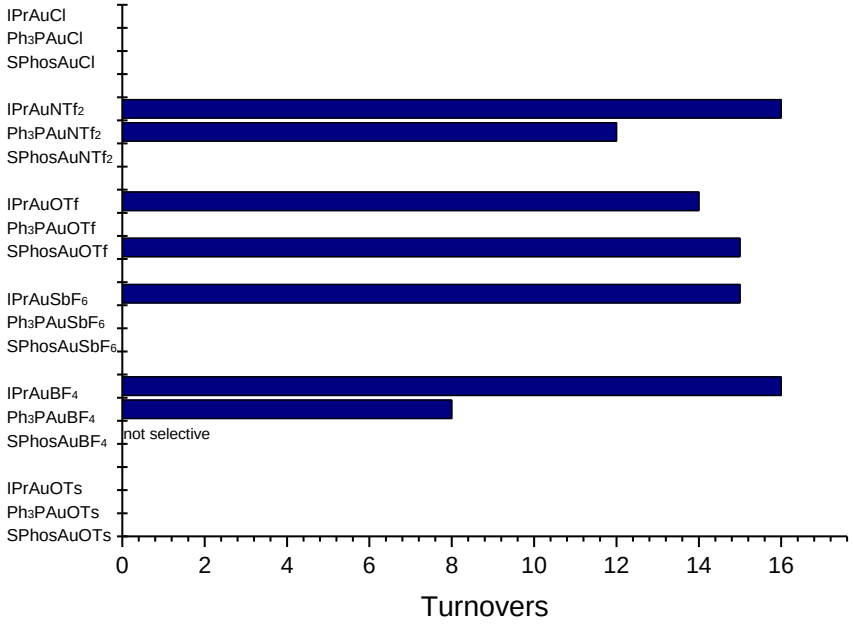

Figure 8. Counter anion influence on an oxidative gold catalysis.

In Figure 9, the strong ligand effect on the investigated oxidative gold catalysis is illustrated. The Buchwald ligand BrettPhos gained an almost complete conversion within the first 15 h. Only the ligand XPhos achieved an almost comparable result but within an extended reaction time of 7 d. Within the monitored reaction time of 14 d phosphites, the CAAC-Cyclohexyl, SPhos, $(C_6F_5)_3P$ as well as the gold(III) complexes showed almost no or no reaction.

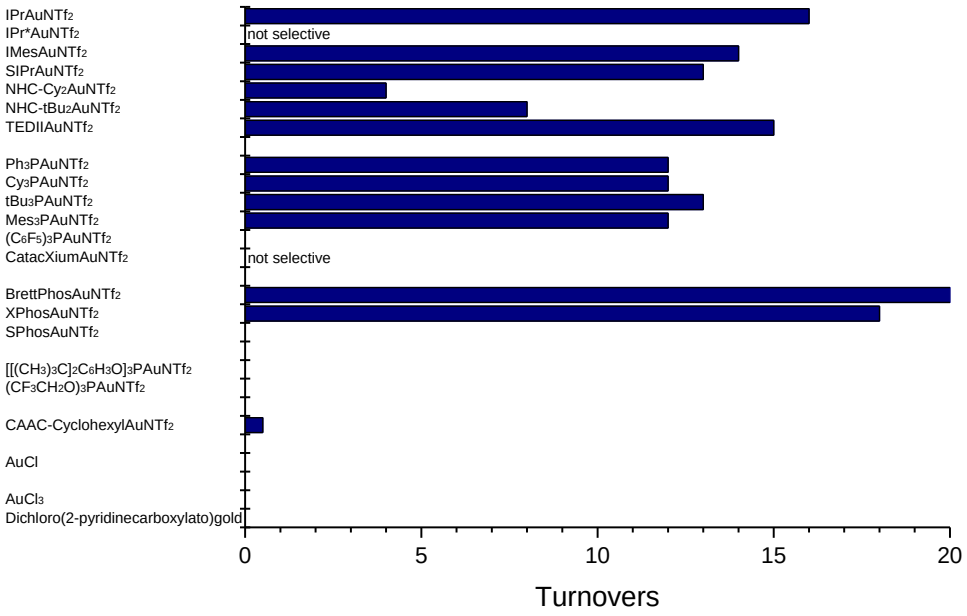

Figure 9. Ligand influence on an oxidative gold catalysis.

The Buchwald ligand BrettPhos (20 turnovers) achieved an almost complete conversion within the first 15 h. Only the ligand XPhos (18 turnovers) achieved an almost comparable result but within an extended reaction time of 7 d. Within the monitored reaction time of 14 d phosphites, the CAAC-Cyclohexyl, SPhos, $(C_6F_5)_3P$ as well as the gold(III) complexes showed a very low or no conversion. In comparison, Zhang and co-workers achieved an almost similar turnover using Me_4*t*BuXPhosAuNTf$_2$ (17 turnovers), however, the reaction times we observed are much higher than the reaction times claimed in the literature.[10b]

Hydroarylation (Scheme 3, Equation 4)

An immense counter anion effect was observed again (Figure 10). The counter anions BF_4^-, OTf^-, NTf_2^- and Cl^- show similar reaction patterns concerning the investigated gold(I) complexes. The best results for each ligand were obtained by far using the counter anion SbF_6^-.

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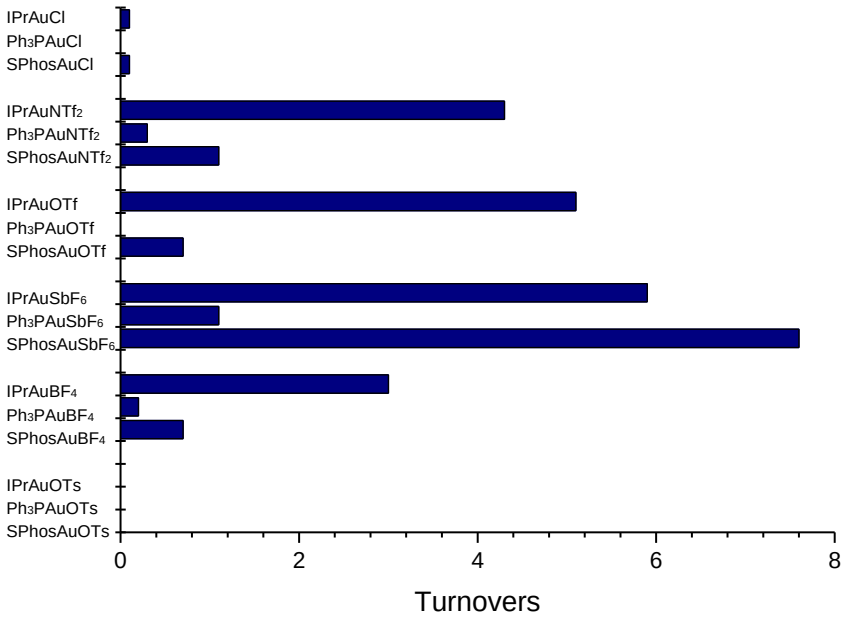

Figure 10. Counter anion influence on the hydroarylation reaction.

Based on a ligand pre-screening by TLC and GC control (see Supporting Information for further details), only selected ligands were analyzed in a further series of experiments. Decomposition of the starting material was observed for most of the investigated ligands. The best result by far was obtained with $(C_6F_5)_3PAuSbF_6$ (Figure 11).

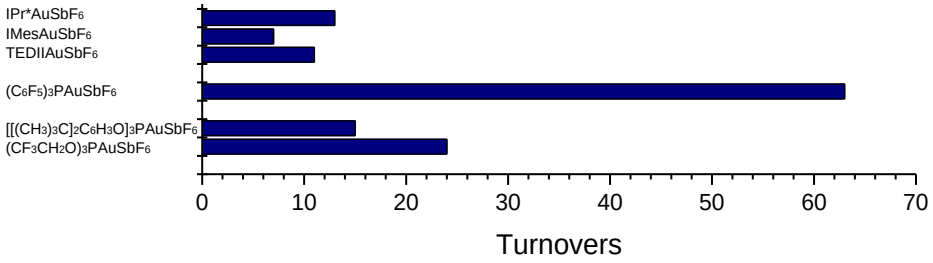

Figure 11. Ligand influence on the hydroarylation reaction.

Again, here we obtained by far the best result reported so far, $(C_6F_5)_3PAuSbF_6$ (63 turnovers, Figure 11). The best catalyst known in the literature only achieved 49 turnovers, this was reported by Alcarazo and co-workers using a polycationic ligand.[10c]

Synthesis of alkylideneoxazoline (Scheme 3, Equation 5)

For the cyclization of propargylamides after a reaction time of 74 h, the TOs show an enhanced dependence on the counter anions. However, the ligand influence is not

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insignificant (Figure 12). Noticeable, in this case no convergence of the results was observed and in this case the best counter anion changed for the applied ligands. In sum, the best catalytic activity was achieved by the counter anion NTf_2^-. Due to this, NTf_2^- was used for the following examinations concerning the ligands (Figure 13).

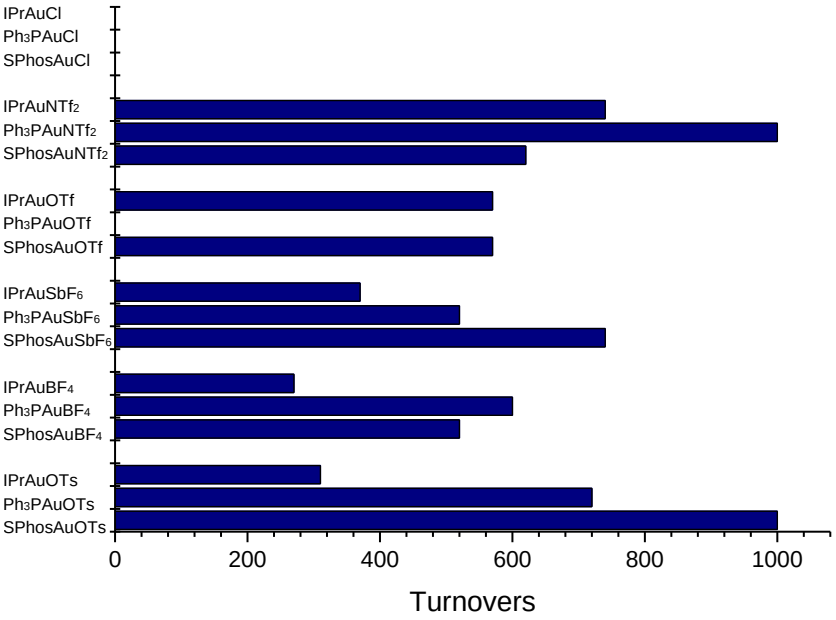


Figure 12. Counter anion influence on the synthesis of alkylideneoxazoline.

Due to the high catalytic activity, the reaction time was decreased from 74 h to 22 h. The results of the best ligands are shown in Figure 13. The examinations show a highly selective reaction, whereby using gold(III) complexes afforded an isomerization of the gained oxazoline to oxazol after an extended time period.[11] However, within a decreased reaction time of 22 h gold(III) complexes as well as $Ph_3PAuNTf_2$ turned out to be the best catalysts and at that stage no isomerization was monitored for the gold(III) species.

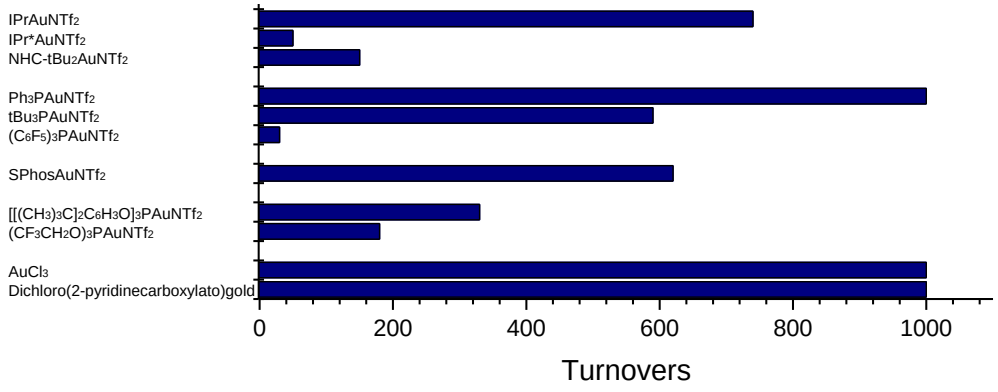


Figure 13. Ligand influence on the synthesis of alkylideneoxazoline.

Again we want to put our results into context. Within a decreased reaction time of only 22 h gold(III) complexes (1000 turnovers) as well as $Ph_3PAuNTf_2$ (1000 turnovers) turned out to be the best catalysts and no isomerization was monitored for the gold(III) catalysts. Probert and co-workers achieved only 50 turnovers using a modified KITPhos ligand in combination with AgOTf as the silver salt.[10e] Hashmi and co-workers used a by $AgPF_6$ for the in situ activation of a gold(I) catalyst based on a hydrazino amino acyclic carbene and achieved only 100 turnovers.[10f,10g]

Conclusion

An intense screening of key reactivity types from various fields of gold catalysis, concerning the ligand and the counter anion of gold catalysts, was conducted. For each test reaction the counter anion significantly affected the catalytic activity. This counter anion influence was mostly more pronounced than the corresponding influence of the ligand. Moreover, for nearly every substrate one or more counter anion showed no or only minor consumption of the substrate. It became obvious that the counter anion influence is still underestimated in experimental homogeneous gold catalysis. In almost all cases the best counter anion for one gold catalyst showed also the highest activity for all investigated ligands; this allowed the establishment of a simplified strategical screening procedure. In a first **Screening A**, we suggest to use a broad set of established silver salts of the counter anions with a limited set of benchmark ligands for an initial identification of the best counter anion. In a second step, **Screening B**, we advise further examinations concerning a large pool of ligands in combination with the superior counter anion from **Screening A**. By following this procedure, the theoretical number of screening experiments which would be necessary to identify the optimal gold catalyst, can be significantly reduced. By means of the cyclopropanation of styrenes by a propargylic pivalate, it was shown that a minimal variation of the substrate leads to significantly different reactivities concerning the counter anion as well as the ligand. Hence, which is no surprise, no general perfect catalyst for a specific reaction exists.

Experimental Section

General remarks

Chemicals were, if not noted otherwise, used from the stock of the University of Heidelberg or were bought from commercial suppliers such as Sigma-Aldrich, Strem and Carbolution. Deuterated solvents were purchased from Euriso-Top. The experiments were carried out in standard laboratory glassware.

NMR (Nuclear magnetic resonance) spectra were recorded at room temperature on Bruker Avance III-300 or Avance DRX-300. ^{1}H NMR spectra were calibrated using the residual solvent signal (CD_2Cl_2: 5.32 ppm).

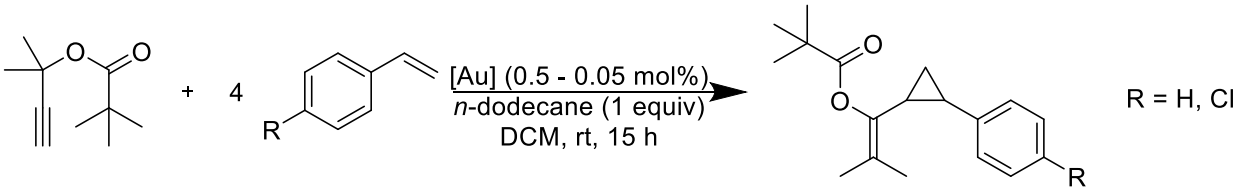
Gas Chromatography (GC) was processed on HP 58090 SERIES II with a HP 1 column. Nitrogen was used as the carrier gas.

Analytical thin layer chromatography (TLC) was carried out on pre-coated aluminum sheets provided by Macherey-Nagel ALUGRAM® Xtra SIL G/UV254. Components were visualized by irradiation under UV light (254 nm).

General procedures

All substrates were isolated according to literature in good to excellent yields.[1-5]

General procedure 1 (GP 1) – GC screening; cyclopropanation of styrene with pivalate



4.6 µl (0.025 mmol; 1 equiv) of 2-methylbut-3-yn-2-yl pivalate was dissolved in 0.5 ml DCM. Afterwards, 11.5 µl (R = H), 12.0 µl (R = Cl) (0.100 mmol; 1 equiv) of freshly distilled styrene, 5.7 µl (0.025 mmol; 1 equiv) of *n*-dodecane and 0.5 mol% (0.125 µmol, 0.005 equiv) of gold catalyst were added to the reaction mixture and the reaction was stirred at room temperature. After a reaction time of 15 h, the gold catalyst was removed via filtration through Silica gel (petroleum ether / ethyl acetate, 1:1) and the reaction sample was analyzed using GC. If an substrate consumption of 100 % was observed within a reaction time of 15 h, the reaction was repeated with a lower catalyst loading.

General procedure 2 (GP 2) – ^{1}H NMR screening; 1,3 rearrangement of an allenylether

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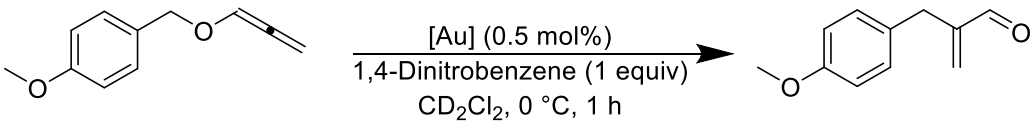
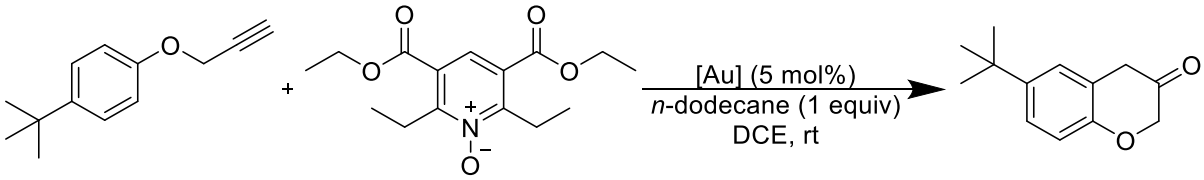


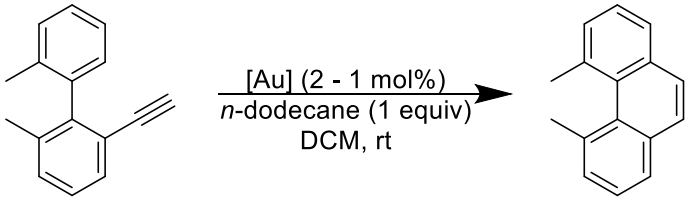
In a NMR tube, 4.0 µl (0.025 mmol; 1 equiv) of 1-methoxy-4-((propa-1,2-dien-1-yloxy)methyl)benzene and 4.2 mg (0.025 mmol; 1 equiv) of 1,4-dinitrobenzene was dissolved in 0.5 ml deuterated DCM. Afterwards, the reaction mixture was cooled to 0 °C and 0.5 mol% (0.125 µmol, 0.005 equiv) of gold catalyst were added. After a reaction time of 1 h at 0 °C, the reaction was analyzed by ^{1}H NMR.

General procedure 3 (GP 3) – GC screening; oxidative gold catalysis using an *N*-oxide



9.3 µl (0.050 mmol; 1 equiv) of 1-(tert-butyl)-4-(prop-2-yn-1-yloxy)benzene, 22.2 mg (0.075 mmol, 1.5 equiv) of diethyl-2,6-diethylpyridin-3,5-dicarboxylate-*N*-oxide and 11.3 µl (0.050 mmol; 1 equiv) of *n*-dodecane were dissolved in 1.0 ml DCE. Afterwards, 5 mol% (0.0025 mmol, 0.05 equiv) of gold catalyst were added to the reaction mixture and the reaction was stirred at room temperature. Because of the extended reaction times, the reaction solution was analyzed after 15 h, 40 h, 7 d and 14 d. Therefore, the gold catalyst was removed via filtration through Silica gel (petroleum ether / ethyl acetate, 1:1) and the reaction sample was monitored using GC.

General procedure 4 (GP 4) – GC screening; hydroarylation



Investigation of the counter anion effect

10 mg (0.048 mmol; 1 equiv) of 2-ethynyl-2',6-dimethyl-1,1'-biphenyl and 11.0 µl (0.048 mmol; 1 equiv) of *n*-dodecane were dissolved in 0.97 ml DCM. Afterwards,

2 mol% (0.97 µmol, 0.02 equiv) of gold catalyst were added to the reaction mixture and the reaction was stirred at room temperature for 4 d. The gold catalyst was removed via filtration through Silica gel (petroleum ether / ethyl acetate, 1:1) and the reaction sample was monitored using GC.

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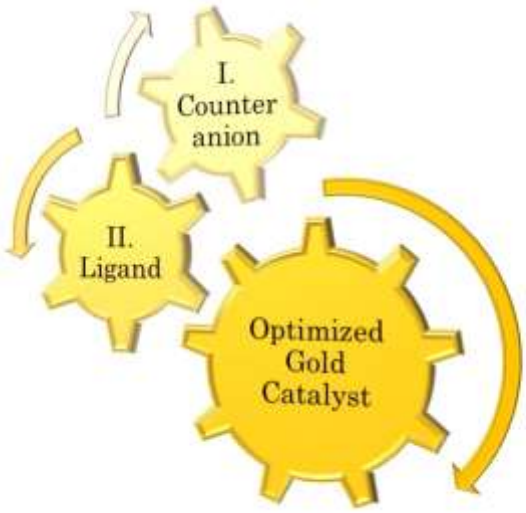
TOC graphic



- strategic guideline for catalyst optimization
- dominant counter anion influence
- remarkable dependency of the substrate on the catalyst reactivity