Sustainable Gold Catalysis in Water Using Cyclodextrin-tagged NHC-Gold Complexes

Hülya Sak,[a] Matthias Mawick,[a] and Norbert Krause*[a]

The synthesis of 10 water-soluble β-cyclodextrin-tagged NHC-gold(I) complexes is described. Key steps are nucleophilic substitutions, as well as, copper-(CuAAC)- and ruthenium-(RuAAC)-catalyzed azide alkyne cycloadditions. Whereas the CuAAC reliably affords 1,4-disubstituted 1,2,3-triazoles, the regioselectivity of the RuAAC depends on the structure of the coupling partners. Permethylated cyclodextrin-tagged NHC-gold(I) complexes are soluble both in water and in organic solvents. They show excellent catalytic activity and recyclability in cyclization reactions of functionalized allenes and alkynes in bulk water. The enantioselective cycloisomerization of γ- and δ-hydroxyallenes could be achieved with up to 38% ee. Thus, it is possible to take advantage of the chirality of the cyclodextrin moiety for enantioselective gold-catalyzed transformations.

Introduction

Organic solvents continue to be the reaction media of choice for transformations of organic substrates, notwithstanding the fact that they are the major source of waste produced by chemists in industry and academia.[1] Numerous alternative solvents with a smaller environmental burden have been introduced in recent years[2] and provide an important contribution to the advancement of *Green Chemistry*.[3] A particularly attractive approach to *Sustainable Chemical Synthesis* is the use of water as reaction medium for catalytic transformations. This can be achieved by using micelles as nanoreactor for substrates and catalysts,[4] or by designing water-soluble catalysts.[5] In the area of homogeneous gold catalysis, we have demonstrated that both strategies[6,7] lead to highly efficient and recyclable catalysts for various transformations in bulk water. A straightforward method to render gold catalysts water-soluble is to decorate them with anionic (carboxylate, sulfonate) or cationic (ammonium) groups.[5,7] For example, NHC-gold(I) catalysts tagged with one or two ammonium salt groups (Figure 1) efficiently catalyze cyclization reactions of various unsaturated substrates in aqueous medium, even in the absence of a silver cocatalyst. The latter is required in organic solvents for generating catalytically active cationic gold species[8] but often has a negative impact on the rate of gold-catalyzed transformations.[8,9]
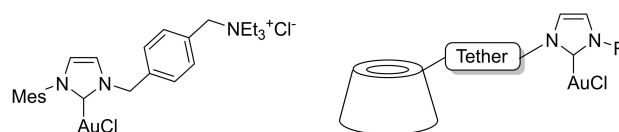

Figure 1. Ammonium salt- and cyclodextrin-tagged NHC-gold(I) catalysts.

A different type of water-soluble catalysts would be obtained by linking a gold-NHC fragment to a cyclodextrin (Figure 1). Cyclodextrins (CD) are cyclic oligomers of glucose which are formed by enzymatic degradation of starch. Due to their unique truncated cone structure with a hydrophobic cavity and a hydrophilic shell, they exhibit a high water solubility and a rich host-guest chemistry.[10] These properties are strongly affected by the size of the cyclodextrin (α-CD/β-CD/γ-CD) and its substituent pattern. Moreover, it is possible to take advantage of the chirality of the cyclodextrin moiety for enantioselective transformations.[11] In this paper, we describe the synthesis of various β-CD-tagged NHC-gold(I) complexes and their use in gold-catalyzed cyclization reactions in bulk water. Key steps for linking the metal fragment to the cyclodextrin are nucleophilic substitutions, as well as, copper-(CuAAC)- or ruthenium-(RuAAC)-catalyzed azide alkyne cycloadditions.

## Results and Discussion

Synthesis by Nucleophilic Substitution

β-Cyclodextrin possesses 7 primary and 14 secondary hydroxy groups. As a consequence, each synthetic procedure starting from the native CD has statistical implications. Our first approach to a cyclodextrin-tagged NHC-gold(I) complex (Scheme 1) started with the monotosylation of β-CD **1** which, besides various multiply tosylated products, afforded the desired monotosylate **2** with 33% yield.[12] Subsequent nucleophilic substitution with N-methylimidazole and anion exchange

[a] Dr. H. Sak, M.Sc. M. Mawick, Prof. Dr. N. Krause
Organic Chemistry
Dortmund University of Technology
Otto-Hahn-Strasse 6
Dortmund D-44227 (Germany)
E-mail: norbert.krause@tu-dortmund.de

This manuscript is part of the Special Issue on the Sustainable and Affordable Chemistry to Meet Future Challenges in the Pharmaceutical Industry.
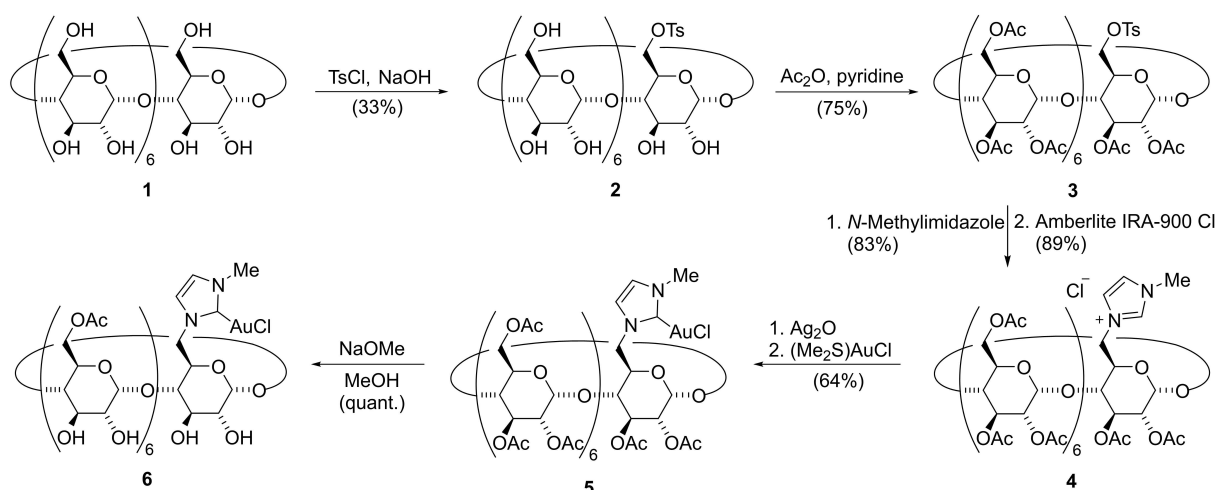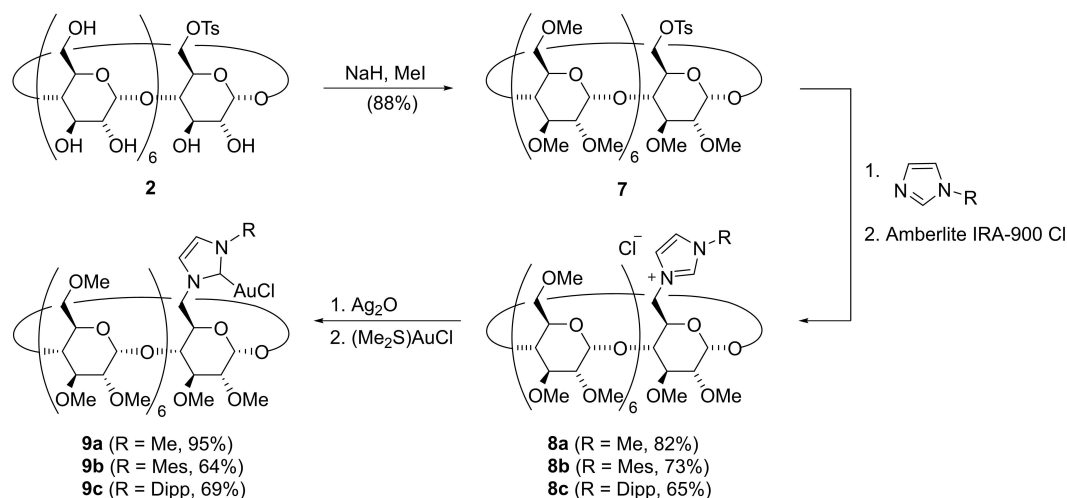
Scheme 1. Synthesis of β-CD-tagged NHC-gold(I) complex **6** by nucleophilic substitution.

with Amberlite® IRA-900 Cl ion exchange resin afforded the corresponding imidazolium chloride. Unfortunately, all attempts to convert this into the corresponding NHC-gold(I) complex in the presence of 20 unprotected hydroxy groups either by Nolan's transmetalation method[13] or via the free NHC obtained by deprotonation with t-BuOK in methanol[7,14,15] failed. A possible reason is the low acidity of the imidazolium ion (pKa ≈ 24),[16] compared to OH groups (pKa ≈ 15). Therefore, the monotosylate **2** was peracetylated to afford **3** with 75 % yield, followed by nucleophilic substitution with N-methylimidazole (83 %) and replacement of the tosylate to chloride using Amberlite® IRA-900 Cl (89 %).

The peracetyled imidazolium chloride **4** thus obtained was converted without problem into the desired β-CD-tagged NHC-gold(I) complex **5** (64 % yield) via the corresponding silver-NHC intermediate.[13] As expected, **5** is soluble in different organic solvents, but not in water. Due to the sensitivity of NHC-gold(I)

compounds towards bases and reducing agents, removal of the acetyl protecting groups is a difficult task. Interestingly, careful treatment of **5** with dilute sodium methanolate solution at ambient temperature liberated all secondary hydroxy groups to afford product **6** in quantitative yield, whereas the six primary OH groups remained acetylated. Attempts to cleave the latter as well resulted in decomposition. NHC-gold(I) complex **6** turned out to be water-soluble and was used for gold-catalyzed cyclization reactions in aqueous medium (see below).

It is well known that partially or fully methylated cyclodextrins can have a remarkably high solubility in water.[10] This effect is caused by removal of intramolecular hydrogen bonds. Therefore, our next approach towards β-CD-tagged NHC-gold(I) complexes (Scheme 2) commenced with the permethylation of tosylate **2** which gave the desired polyether **7** with 88 % yield. The following steps were performed as previously. For the nucleophilic substitution, three sterically different imidazole

Scheme 2. Synthesis of permethylated β-CD-tagged NHC-gold(I) complexes **9 a–c** by nucleophilic substitution.

derivatives bearing methyl, mesityl (Mes), or 2,6-diisopropyl (DIPP) groups were used. After anion exchange, the imidazolium chlorides **8a–c** were isolated with 65–82% yield. The final conversion into the gold complexes **9a–c** took place with good yield (64–95%) as well. Excellent solubility of the latter in organic solvents, as well as, in water was observed. Thus, 4 different water-soluble β-CD-tagged NHC-gold(I) complexes (**6**, **9a**, **9b**, **9c**) were efficiently synthesized by nucleophilic substitution.

Synthesis by Copper-Catalyzed Azide Alkyne Cycloaddition (CuAAC)

The 1,3-dipolar cycloaddition of alkynes and organic azides was developed as a thermal reaction by Huisgen.[17] Its copper-catalyzed variant (CuAAC) has become the most widely used example of click chemistry since it shows excellent reactivity and regioselectivity in favor of 1,4-disubstituted triazoles.[18] Several applications of the CuAAC for the synthesis of functionalized cyclodextrin derivatives have been reported.[19] Recently, we have used the CuAAC as key step for the synthesis of a biotin-tagged NHC-gold(I) catalyst.[15] Hence, it appeared promising to apply this method to the assembly of β-CD-tagged NHC-gold(I) complexes as well.

We started our approach with propargyl ether **10** which is readily accessible be treating propargyl alcohol with sodium hydride and permethylated tosylate **7** (Scheme 3). The coupling partner, azido-substituted imidazolium salt **11**, was synthesized before by our group.[15] Several different copper salts (CuBr, CuI, CuSO₄, Ph₃PCuI, (EtO)₃PCuI[20]) in the presence or absence of additives (sodium ascorbate, ascorbic acid, DIPEA, TBTA[20]) and DMF, DMSO, THF or *t*BuOH (pure or mixed with water) as

solvent were tested and afforded click product **12** with no more than 31% yield. A much better result was obtained when we used CuI/DIPEA in a mixture of MeCN and EtOAc; this gave **12** with 71% after 2 d at room temperature (see Supporting Information for details). The 1,4-regioselectivity of the click reaction was proven by extensive NMR studies, in particular with ¹H-¹⁵N-HMBC experiments (see Supporting Information). Once again, Nolan's transmetalation method proved itself nicely for generating the water soluble triazole-linked β-CD-tagged NHC-gold(I) complex **13** with 74% yield.

Next, we synthesized structurally simpler triazole-linked cyclodextrin-tagged gold catalysts by using the azido-substituted imidazolium bromides **14a/b** as coupling partner for alkyne **10** (Scheme 4). These were obtained by treating 1,2-dibromoethane with mesityl- or ethylimidazole and sodium azide. Using the best conditions for the synthesis of **12** gave no conversion at room temperature, and only traces of click product **15a** at 50 °C. Thus, careful optimization of the reaction conditions for the CuAAC was required once again. It turned out that an excess of CuI and the addition of sodium ascorbate had a beneficial effect on this particular click reaction, affording imidazolium salt **15a** with 65% yield after 2 d at 80 °C. Interestingly, only traces of triazole **15b** were obtained from coupling partners **14b** and **10** under these conditions. In this case, lowering the amount of CuI and decreasing the temperature to room temperature provided the best yield of 26%. ¹H-¹⁵N-HMBC experiments revealed that also these coupling products bear a 1,4-disubstituted triazole linker. Conversion of **15a/b** to the NHC-gold(I) compounds by treatment with Ag₂O and (Me₂S)AuCl afforded only traces of the mesityl-substituted complex **16a**, whereas its ethyl-substituted counterpart **16b** could be isolated with 52% yield.
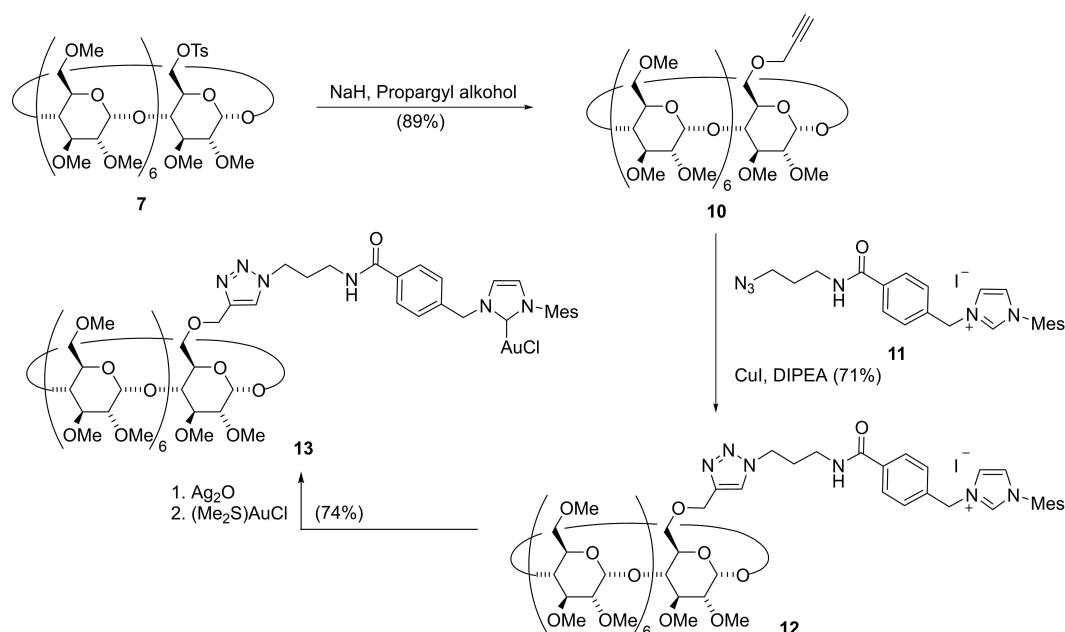
Scheme 3. Synthesis of β-CD-tagged NHC-gold(I) complex **13** by CuAAC of propargyl ether **10** and azide **11**.
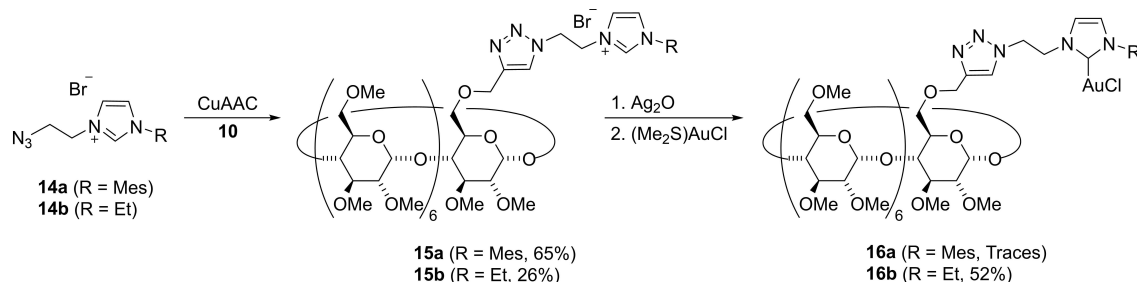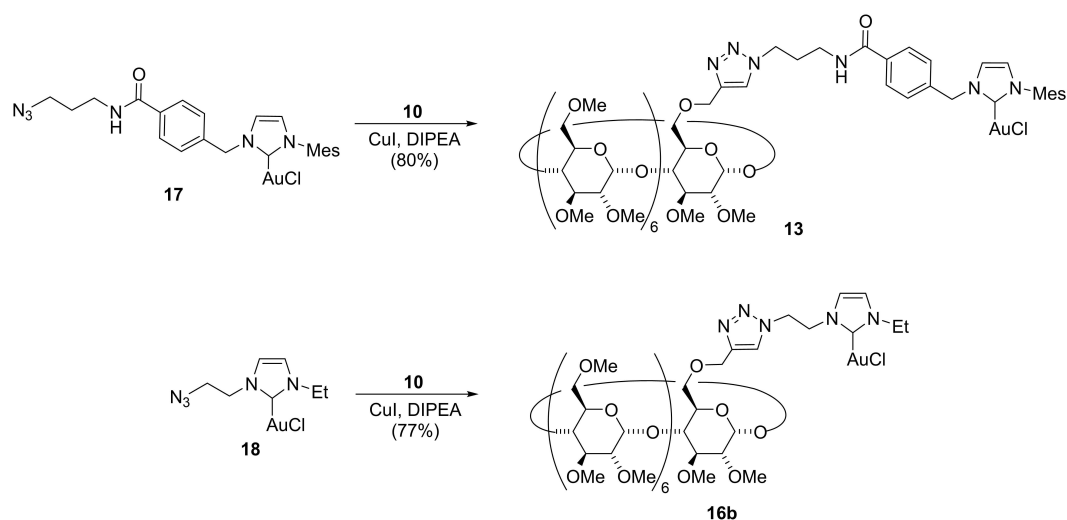
Scheme 4. Synthesis of β-CD-tagged NHC-gold(I) complexes **16 a/b** by CuAAC of propargyl ether **10** and azides **14 a/b**.

During our previous synthesis of a biotin-tagged NHC-gold (I) catalyst, we have demonstrated that a NHC-gold(I) complex is not stable under CuAAC conditions, but undergoes decomposition with formation of a gold mirror.[15] In order to determine whether this is a general behavior, we synthesized azido-substituted NHC-gold(I) complexes **17**[15] and **18** from the imidazolium salts **11** and **14 b**,[21] respectively, and used them in the copper-catalyzed click reaction with β-CD-derived propargyl ether **10** (Scheme 5). To our delight, the desired triazoles **13** and **16 b** were obtained with high yield in the presence of CuI/ DIPEA in MeCN/EtOAc. Thus, reversing the order of CuAAC and NHC-gold(I) complex formation can lead to beneficial results.

In order to further increase the structural diversity of the cyclodextrin-tagged gold complexes, we reversed the role of the coupling partners (Scheme 6). The required azide **19** was obtained with 87% yield by treating permethylated tosylate **7** with sodium azide in the presence of potassium iodide. The latter accelerated the nucleophilic substitution by formation of the corresponding iodide. The propargyl ester **20** has been synthesized previously[15] and could be coupled with **19** in the presence of CuSO₄ and sodium ascorbate to afford **21** with high yield (86%). Once again, ¹H-¹⁵N-HMBC experiments proved the regioselectivity of the click reaction in favor of the 1,4-disubstituted triazole. The final transformation of **21** into the

desired β-CD-tagged NHC-gold(I) complex **22** was achieved with 83% yield under standard conditions.

In a similar manner, the NHC-gold(I) complex **25** bearing two short methylene linkers was obtained (Scheme 7). The required propargyl-substituted imidazolium salt **23** is readily available by reaction of mesitylimidazole with propargyl bromide. With CuSO₄ and sodium ascorbate, click product **24** was formed with only 25% yield. By contrast, the use of CuI/ DIPEA in the presence of sodium ascorbate afforded the 1,4-disubstituted triazole **24** with 83% yield. Formation of NHC-gold(I) complex **25** (68% yield) proceeded smoothly. Overall, we were able to synthesize 4 different water-soluble β-CD-tagged NHC-gold(I) complexes (**13**, **16 b**, **22**, **25**) by copper-catalyzed azide alkyne cycloaddition (CuAAC). Even azido-substituted NHC-gold(I) complexes (**17**, **18**) can be used as coupling partner. Although these click reactions usually afford the desired 1,4-disubstituted triazoles with good yield, it should be noted that the reaction conditions have to be optimized starting from scratch for each combination of the reactants.

Scheme 5. Synthesis of β-CD-tagged NHC-gold(I) complexes **13** and **16 b** by CuAAC of propargyl ether **10** and gold complexes **17/18**.
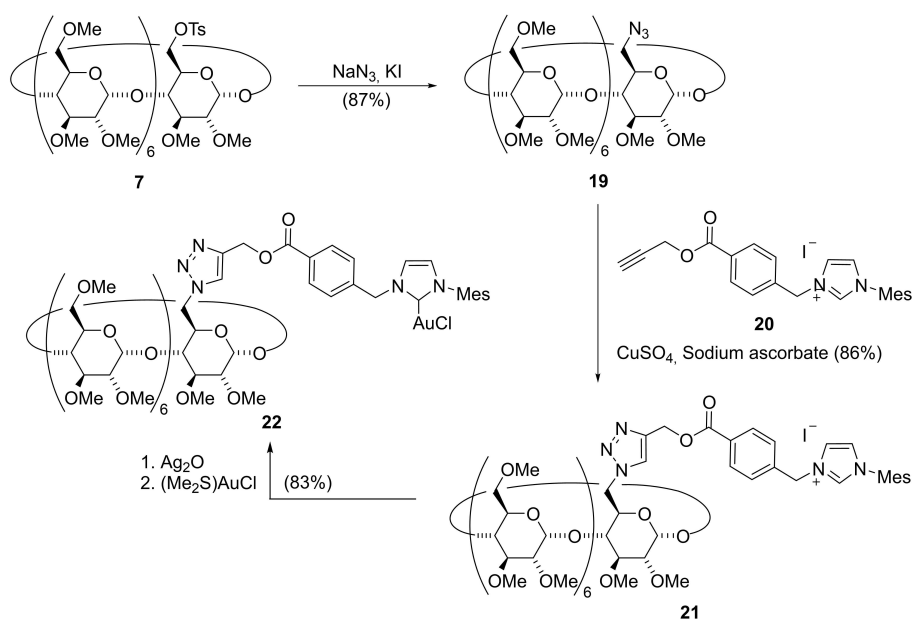
Scheme 6. Synthesis of β-CD-tagged NHC-gold(I) complex **22** by CuAAC of azide **19** and propargyl ether **20**.
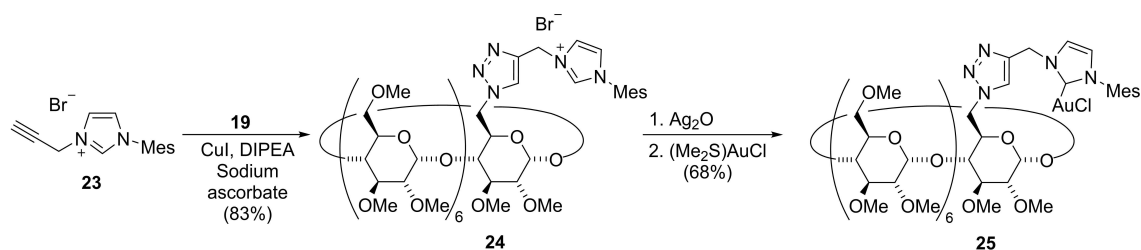
Scheme 7. Synthesis of β-CD-tagged NHC-gold(I) complex **25** by CuAAC of azide **19** and alkyne **23**.
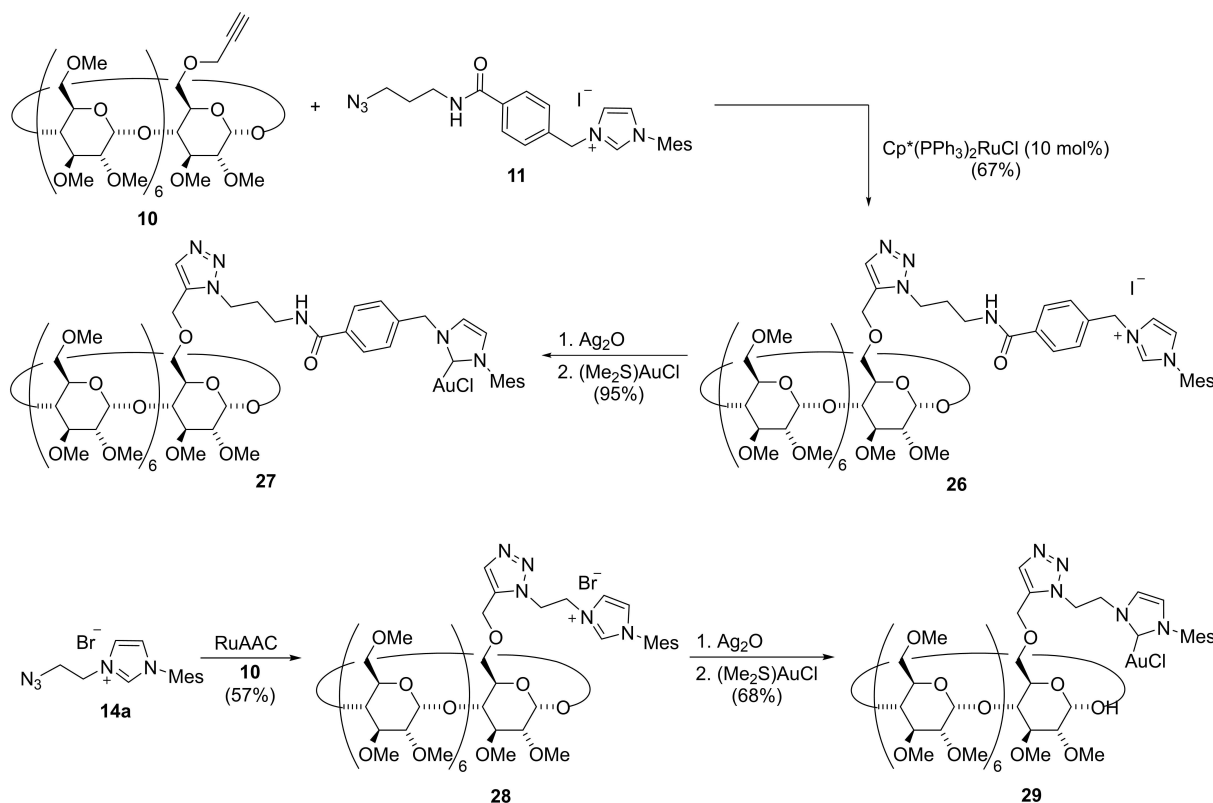
Synthesis by Ruthenium-Catalyzed Azide Alkyne Cycloaddition (RuAAC)

The use of ruthenium catalysts for 1,3-dipolar cycloadditions of alkynes and organic azides was introduced by Fokin and Jia in 2005.[22] In contrast to the copper-catalyzed variant, which reliably affords 1,4-disubstituted triazoles, the ruthenium-catalyzed azide alkyne cycloaddition (RuAAC) provides an access to the 1,5-disubstituted regioisomers, in particular when sterically demanding ruthenium catalysts are used. The complementarity to the CuAAC, as well as, the tolerance to various functional groups, and the use of internal alkynes as coupling partner have led to numerous applications of the RuAAC in many different areas.[23] Thus, it seemed intriguing to utilize this method for the synthesis of water-soluble β-CD-tagged NHC-gold(I) complexes.

With various coupling partners in hand, we first examined the RuAAC of azido-substituted cyclodextrin derivative **19** with propargyl ester **20**. Heating of the coupling partners with 10 mol% Cp*Ru(PPh₃)₂Cl in DMF to 120 °C for 2 d afforded the click product with 39% yield. Careful spectroscopic analysis, in particular with ^{1}H–^{15}N–HMBC experiments, revealed that a

70:30-mixture of the 1,4-disubstituted triazole **21** (Scheme 6) and its 1,5-regioisomer was formed under these conditions. The regioselectivity could not be improved by variation of the reaction conditions. Under the same conditions, but with microwave heating to 120 °C for 5 h, the click reaction of **19** with azide **23** gave the 1,4-disubstituted regioisomer **24** (Scheme 7) as only product with 73% yield. All spectral data, including the ^{1}H-^{15}N-HMBC spectrum, are identical to those of the triazole obtained by CuAAC.

The strong influence of the substrate structure on the regioselectivity of the RuAAC was further demonstrated in click reactions of alkynyl-substituted cyclodextrin derivative **10** with azido-substituted imidazolium salts (Scheme 8). Thus, the desired coupling product **26** was obtained with 67% yield by heating of a mixture of **10** and **11** in the presence of 10 mol% Cp*Ru(PPh₃)₂Cl in DMF to 120 °C for 2 d. Likewise, microwave heating to 120 °C for 5 h converted a mixture of **10**, azide **14a**, and Cp*Ru(PPh₃)₂Cl (10 mol%) in DMF into the 1,5-disubstituted triazole **28** which was isolated with 57% yield. The corresponding water-soluble β-CD-tagged NHC-gold(I) complexes **27** and **29** were formed with good to excellent yield from **26** and **28**, respectively, under Nolan's conditions. Thus,

Scheme 8. Synthesis of β-CD-tagged NHC-gold(I) complexes **27** and **29** by RuAAC of propargyl ether **10** and azides **11** and **14 a**.

we have demonstrated that the ruthenium-catalyzed azide alkyne cycloaddition (RuAAC) is a suitable method for the coupling of cyclodextrin and imidazolium fragments. Compared to the copper-catalyzed method, strong heating is required, and the regioselectivity depends on the structure of the coupling partners. However, an extensive optimization of the reaction conditions is not required for the RuAAC.

For the structural assignment of the products obtained by copper- or ruthenium catalyzed azide alkyne cycloaddition, the analysis of ^{1}H-^{15}N-HMBC spectra is indispensable. These detect couplings between nitrogen atoms and protons over 2, 3, or 4 bonds. As an example, Figure 2 shows these spectra for the 1,4-disubstituted triazole **15 a** and its 1,5-regioisomer **28**. As expected, couplings between the imidazolium nitrogen atoms a/a* and the protons in position 1, 2, 3, 4, and 5 are observed for both isomers. For isomer **15 a**, nitrogen atom b couples with the triazole proton 7-H, as well as, with the methylene protons in position 6. The interaction of nitrogen atom d with 7-H, and in particular with the diastereotopic protons 8-H proves the connectivity of this 1,4-disubstituted triazole. Nitrogen atom c only undergoes long-range couplings and is not observed. By contrast, nitrogen atom b of isomer **28** couples with 7-H and with both 6-H and 8-H. Moreover, nitrogen atoms c and d only couple with the triazole proton 7-H. These observations prove the 1,5-disubstitution of **28**.

Gold-catalyzed Cyclization Reactions

In this paper, we have described the syntheses of 10 water-soluble β-CD-tagged NHC-gold(I) complexes (**6**, **9 a**, **9 b**, **9 c**, **13**, **16 b**, **22**, **25**, **27**, **29**) with a wide structural diversity. These were achieved by using different key reactions (nucleophilic substitution, CuAAC, RuAAC) for coupling the cyclodextrin moiety to the NHC fragment via tethers of variable length and flexibility. The next step was to examine the reactivity and recyclability of the new gold catalysts in transformations of unsaturated substrates in bulk water. As benchmark reactions, we selected the cycloisomerization of α-hydroyallene **30** to 2,5-dihydrofuran **31**,[6,7a,24] as well as, the intramolecular lactonization of pent-4-ynoic acid **32** to **33** (Scheme 9).[7b,25] Initially, we examined the cyclization of allene **30** in the presence of the 4
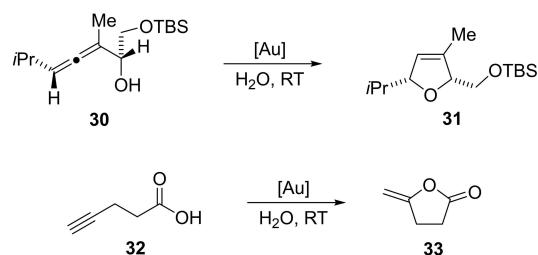
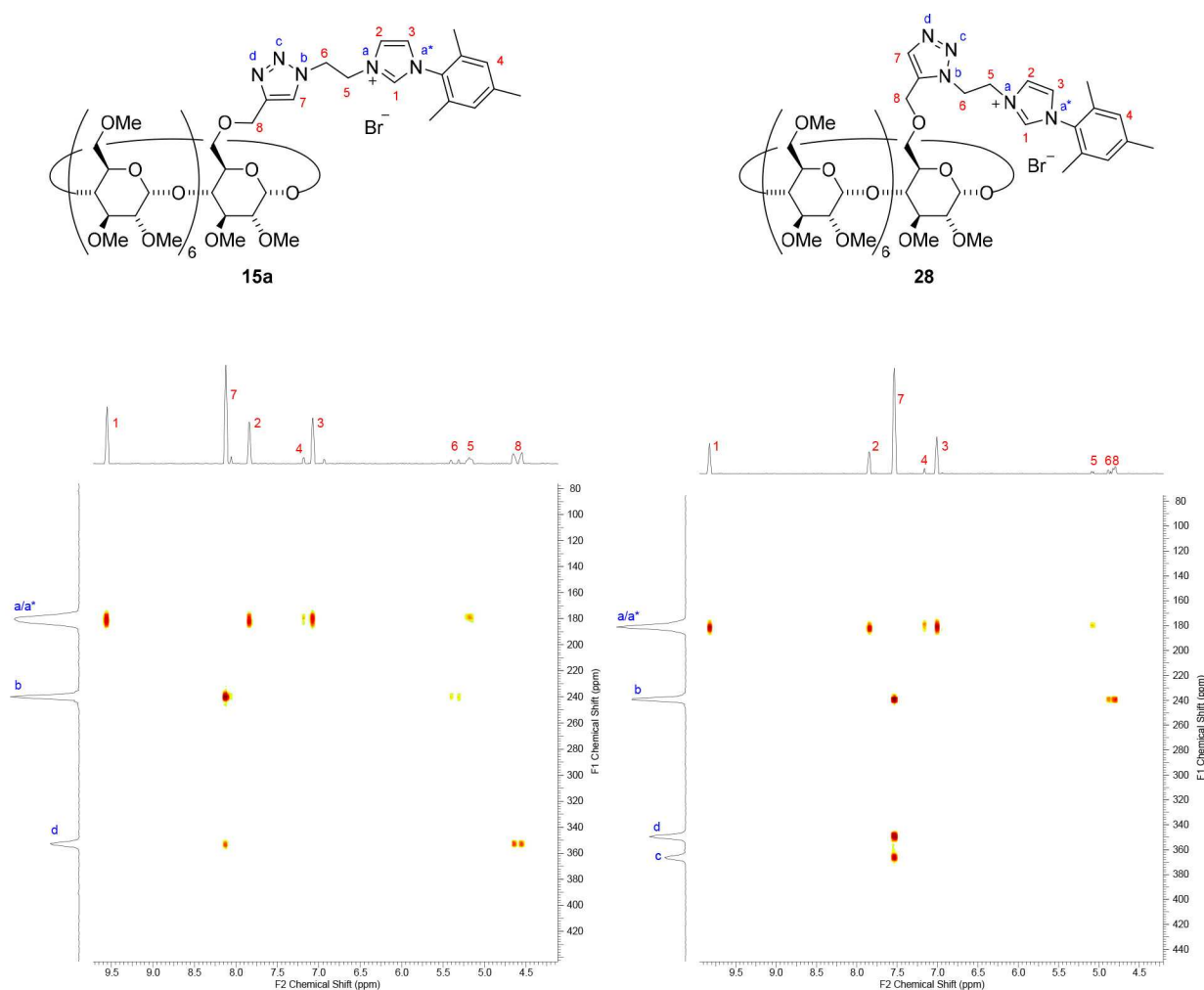**Scheme 9.** Gold-catalyzed cyclization reactions in aqueous medium.

Figure 2. ^{1}H-^{15}N-HMBC spectra of β-CD-tagged imidazolium salts **15a** and **28**.

NHC-gold(I) complexes obtained by nucleophilic substitution (**6**, **9a**, **9b**, **9c**) under standard conditions (5 mol% catalyst, water, room temperature, 24 h; Table 1).

All 4 gold complexes are catalytically active in the allene cyclization. However, full conversion was only observed for catalyst **9a** (Table 1, entry 2), whereas the other catalysts gave 54–85% conversion after 24 h at room temperature. These results show that the presence of free hydroxy groups at the cyclodextrin is not required for an active, water soluble gold catalyst. Interestingly, the addition of a silver salt increased the reactivity of catalyst **6** (Table 1, entry 1), while the activity of the other complexes remained virtually unchanged. A control experiment in the absence of a gold catalyst revealed a negligible catalytic activity of the silver salt alone (Table 1, entry 5).

Next, we investigated the recyclability of gold complexes **9a**, **13**, **16b**, **22**, **25**, **27**, and **29** under standard conditions in the presence or absence of a silver additive (Table 2). After each run, the product was removed by extracting the reaction mixture with pentane and diethyl ether, followed by addition of a new batch of allene **30** to the aqueous catalyst solution. Interestingly, catalyst **9a** showed a strong decrease of reactivity over few cycles in the presence of silver salts (Table 2, entries 1–3); this effect was particularly pronounced with AgBF$_4$ (Table 2, entry 3). In contrast, only a small activity loss was observed in the absence of a silver additive (Table 2, entry 4). Under these conditions, all other β-CD-tagged NHC-gold(I) complexes prepared in this work also exhibit excellent reactivity and recyclability in the cycloisomerization of allenol **30** to dihydrofuran **31** in water (Table 2, entries 5–10). The best performance

Table 1. Gold-catalyzed cycloisomerization of α-hydroxyallene **30** in water.[a]

Entry	[Au]	Conversion [%]	Conversion with AgOTf[b] [%]
1	**6**	54	91
2	**9a**	>99	>99
3	**9b**	85	82
4	**9c**	81	79
5	–	–	<1

[a] 5 mol% gold catalyst, RT, 24 h; conversions were determined by FID-GC, [b] 5 mol% AgOTf.

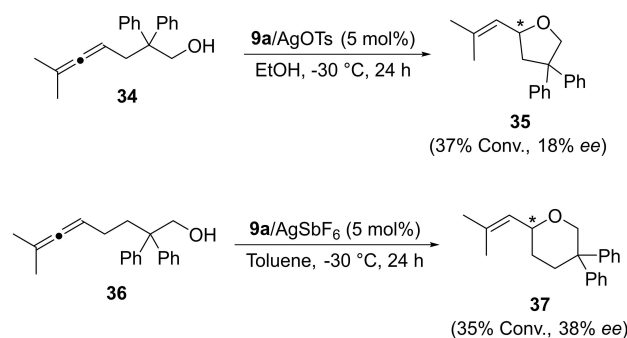**Table 2.** Recycling of the gold catalyst in the cycloisomerization of α-hydroxyallene **30** in water.[a]

Entry	[Au]	Additive[b]	Run 1	2	3	4
1	**9a**	AgOTf	>99	86	30	8
2	**9a**	AgSbF$_6$	84	55	31	12
3	**9a**	AgBF$_4$	38	5	–	–
4	**9a**	–	>99	>99	97	89
5	**13**	–	>99	82	72	–
6	**16b**	–	99	81	78	–
7	**22**	–	97	96	80	–
8	**25**	–	98	91	88	–
9	**27**	–	98	87	79	–
10	**29**	–	99	91	82	–

[a] 5 mol% gold catalyst, RT, 24 h; Conversions were determined by FID-GC, [b] 5 mol% additive.

Scheme 10. Enantioselective gold-catalyzed cycloisomerization of γ- and δ-hydroxyallenes.

was observed for catalysts **22** and **25**, even though the differences are small. Various scenarios for the negative impact of silver salts in gold-catalyzed transformations have been discussed in the literature, including the formation of catalytically inactive multinuclear complexes.[8,9] Thus, the activity of water-soluble cyclodextrin-tagged NHC-gold(I) complexes in the absence of a silver additive (which may be due to formation of catalytically active cationic gold species by spontaneous dissociation of NHC-gold(I) chlorides in bulk water) is a tremendous advantage.

Compared to the allene cyclization, the reactivity of the intramolecular lactonization of pent-4-ynoic acid (Scheme 9) is so high that full conversion is observed in the presence of 2.5 mol% of catalyst **9a** in water after only 15 min at room temperature. After product extraction, the aqueous catalyst solution could be recycled four times. However, the reaction time had to be increased from 15 min (run 1) to 60 min (run 4) in order to achieve full conversion. Thus, it appears that a slight leaching and/or decomposition of the catalyst by the acidic reaction medium is taking place.[7b] All other β-CD-tagged NHC-gold(I) complexes also show excellent catalytic activity and recyclability in this lactonization, without formation of an alkyne hydration side product.[7a,25]

Finally, we tried to utilize the chirality of β-CD-tagged NHC-gold(I) complexes in enantioselective transformations. Enantioselective cycloisomerizations of prochiral γ- or δ-hydroxyallenes to the corresponding tetrahydrofurans or –pyrans in the presence of chiral gold catalysts have been described by Widenhoefer and Toste.[26] In proof-of-principle experiments, we used the chiral NHC-gold(I) catalyst **9a** for the cyclization of the prochiral allenols **34** and **36** (Scheme 10). Whereas only racemic products **35** and **37** were formed in aqueous medium, enantioselective cyclizations could be performed in organic solvents. Under these conditions, activation of the NHC-gold(I) chloride with a silver salt is essential for achieving catalytic activity. Thus, treatment of **34** with 5 mol% **9a** and AgOTs in ethanol for 24 h furnished tetrahydrofuran **35** with 18% *ee*. The corresponding cyclization of allene **36** with AgSbF$_6$ as additive and toluene as solvent gave chiral tetrahydropyran **37** with 38% *ee*. Even though both the conversion and the enantiose-

lectivity of these reactions are far away from being preparatively useful, they demonstrate that the chirality of cyclodextrin-tagged gold catalysts can indeed be used in stereoselective synthesis. It should be noted that the high solubility of permethylated cyclodextrin derivatives both in water and in organic solvents is a huge benefit for these applications.

Conclusions

In this paper, the synthesis of 10 β-cyclodextrin-tagged NHC-gold(I) complexes and their application in cyclization reactions of unsaturated substrates both in organic solvents and in water are described. Key structural features of these complexes are a tether of variable length and flexibility between the cyclodextrin and NHC-gold moiety, as well as, different steric properties at the N-heterocyclic carbene. The coupling between the fragments was achieved by nucleophilic substitutions, as well as, copper-(CuAAC)- and ruthenium-(RuAAC)-catalyzed azide alkyne cycloadditions. Whereas the CuAAC reliably affords 1,4-disubstituted 1,2,3-triazoles, the regioselectivity of the RuAAC depends on the structure of the coupling partners. Even azido-substituted NHC-gold(I) complexes can be used in the click reactions. The regioselectivity of the 1,3-dipolar cycloadditions was determined with the aid of ^{1}H-^{15}N-HMBC spectra. The new β-cyclodextrin-tagged NHC-gold(I) complexes show excellent catalytic activity and recyclability in cyclization reactions of functionalized allenes and alkynes in bulk water. Moreover, enantioselective cycloisomerizations of γ- and δ-hydroxyallenes could be achieved with up to 38% *ee*, taking take advantage of the chirality of the cyclodextrin moiety. Further work is devoted to the fine-tuning of CD-tagged NHC-gold catalysts by variation of the size and substitution pattern of the cyclodextrin, as well as, the complexation properties of the complexes, including the possibility of self-complexation.

Experimental Section

Experimental Details are given in the Supporting Information.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: cyclodextrins · gold catalysis · green chemistry · click reactions · recyclable catalysts

[1] B. H. Lipshutz, F. Gallou, S. Handa, *ACS Sustainable Chem. Eng.* **2016**, *4*, 5838–5849.

[2] a) R. A. Sheldon, *Green Chem.* **2005**, *7*, 267–278; b) Q. Chu, M. S. Yu, D. P. Curran, *Tetrahedron* **2007**, *63*, 9890–9895; c) D. A. Alonso, A. Baeza, R. Chinchilla, G. Guilena, I. M. Pastor, D. J. Ramón, *Eur. J. Org. Chem.* **2016**, *2016*, 612–632.

[3] a) P. T. Anastas, J. C. Warner, *Green Chem.*, Oxford University Press, New York, **1998**; b) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312.

[4] a) B. H. Lipshutz, S. Ghorai, *Green Chem.* **2014**, *16*, 3660–3679; b) G. La Sorella, G. Strukul, A. Scarso, *Green Chem.* **2015**, *17*, 644–683; c) N. Krause, *Curr. Opin. Green. Sustain. Chem.* **2017**, *7*, 18–22.

[5] a) W. A. Herrmann, C. W. Kohlpaintner, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1524–1544; b) L.-A. Schaper, S. J. Hock, W. A. Herrmann, F. E. Kühn, *Angew. Chem. Int. Ed.* **2013**, *52*, 270–289; *Angew. Chem.* **2013**, *125*, 284–304.

[6] Micellar gold catalysis: a) S. R. K. Minkler, B. H. Lipshutz, N. Krause, *Angew. Chem. Int. Ed.* **2011**, *50*, 7820–7823; *Angew. Chem.* **2011**, *123*, 7966–7969; b) S. R. K. Minkler, N. A. Isley, D. J. Lippincott, N. Krause, B. H. Lipshutz, *Org. Lett.* **2014**, *16*, 724–726; c) L. Lempke, A. Ernst, F. Kahl, R. Weberskirch, N. Krause, *Adv. Synth. Catal.* **2016**, *358*, 1491–1499; d) See also: S. Handa, D. J. Lippincott, D. H. Aue, B. H. Lipshutz, *Angew. Chem. Int. Ed.* **2014**, *53*, 10658–10662; *Angew. Chem.* **2014**, *126*, 10834–10838.

[7] Water-soluble gold catalysts: a) K. Belger, N. Krause, *Eur. J. Org. Chem.* **2015**, *2015*, 220–225; b) K. Belger, N. Krause, *Org. Biomol. Chem.* **2015**, *13*, 8556–8560.

[8] Z. Lu, G. B. Hammond, B. Xu, *Acc. Chem. Res.* **2019**, *52*, 1275–1288.

[9] a) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012–9019; b) A. Zhdanko, M. E. Maier, *ACS Catal.* **2015**, *5*, 5994–6004.

[10] a) J. Szejtli, *Chem. Rev.* **1998**, *98*, 1743–1754; b) K. Uekama, F. Hirayama, T. Irie, *Chem. Rev.* **1998**, *98*, 2045–2076; c) J. Szejtli, *Pure Appl. Chem.* **2004**, *76*, 1825–1845; d) D. Prochowicz, A. Kornowicz, J. Lewiński, *Chem. Rev.* **2017**, *117*, 13461–13501.

[11] a) Y. T. Wong, C. Yang, K.-C. Ying, G. Jia, *Organometallics* **2002**, *21*, 1782–1787; b) A. Schlatter, M. K. Kundu, W.-D. Woggon, *Angew. Chem. Int. Ed.* **2004**, *43*, 6731–6734; *Angew. Chem.* **2004**, *116*, 6899–6902; c) M. Guitet, P. Zhang, F. Marcelo, C. Tugny, J. Jiménez-Barbero, O. Buriez, C. Amatore, V. Mouriès-Mansuy, J.-P. Goddard, L. Fensterbank, Y. Zhang, S. Roland, M. Ménand, M. Sollogoub, *Angew. Chem. Int. Ed.* **2013**, *52*, 7213–7218; *Angew. Chem.* **2013**, *125*, 7354–7359; d) Z. Kaya, L. Andna, D. Matt, E. Bentouhami, J.-P. Djukic, D. Armspach, *Chem. Eur. J.* **2018**, *24*, 17921–17926; e) Z. Kaya, L. Andna, D. Matt, E. Bentouhami, J.-P. Djukic, D. Armspach, *Eur. J. Org. Chem.* **2019**, *2019*, 4528–4537.

[12] M. Raoov, S. Mohamad, M. R. Abas, *Int. J. Mol. Sci.* **2014**, *15*, 100–119.

[13] A. Collado, A. Gomez-Suarez, A. R. Martin, A. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2013**, *49*, 5541–5543.

[14] W. Wang, J. Wu, C. Xia, F. Li, *Green Chem.* **2011**, *13*, 3440–3445.

[15] V. Breker, H. Sak, G. Baracchi-Krause, N. Krause, *Tetrahedron Lett.* **2015**, *56*, 3390–3392.

[16] R. W. Alder, P. R. Allen, S. J. Williams, *J. Chem. Soc. Chem. Commun.* **1995**, 1267–1268.

[17] R. Huisgen, R. Knorr, L. Möbius, G. Szeimies, *Chem. Ber.* **1965**, *98*, 4014–4021.

[18] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056–2075; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; *Angew. Chem.* **2002**, *114*, 2708–2711; c) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; d) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952–3015; e) L. Y. Liang, D. Astruc, *Coord. Chem. Rev.* **2011**, *255*, 2933–2945; f) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905–4979.

[19] a) Y. Wang, Y. Xiao, T. T. Y. Tan, S.-C. Ng, *Tetrahedron Lett.* **2008**, *49*, 5190–5191; b) M. Mourer, F. Hapiot, E. Monflier, S. Menuel, *Tetrahedron* **2008**, *64*, 7159–7163; c) S. Srinivasachari, T. M. Reineke, *Biomaterials* **2009**, *30*, 928–938.

[20] T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V. Fokin, *Org. Lett.* **2004**, *6*, 2853–2855.

[21] Treatment of imidazolium salt **14a** with Ag$_2$O und (Me$_2$S)AuCl gave only traces of the corresponding NHC-gold(I) complex.

[22] L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999.

[23] J. R. Johansson, T. Beke-Somfai, A. S. Stålsmeden, N. Kann, *Chem. Rev.* **2016**, *116*, 14726–14768.

[24] a) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537–2538; b) C. Deutsch, B. Gockel, A. Hoffmann-Röder, N. Krause, *Synlett* **2007**, 1790–1794; c) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994–2009.

[25] a) E. Thomás-Mendivil, P. Y. Toullec, J. Díez, S. Conejero, V. Michelet, V. Cadierno, *Org. Lett.* **2012**, *14*, 2520–2523; b) E. Thomás-Mendivil, P. Y. Toullec, J. Borge, S. Conejero, V. Michelet, V. Cadierno, *ACS Catal.* **2013**, *3*, 3086–3098.

[26] a) Z. Zhang, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2007**, *46*, 283–285; *Angew. Chem.* **2007**, *119*, 287–289; b) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496–499.