Indium Versus Gold Catalysis in Dehydrative Reactions with Allylic Alcohols

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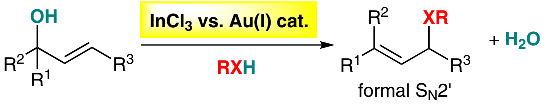


- superior chemoselectivity: pendent C–C π bonds better tolerated by In(III)
- cheaper catalyst, higher yields
- 11 examples with each catalyst (up to 97% yield)

Received: 17.08.2015
Accepted after revision: 14.09.2015

DOI: 10.1055/s-0035-1560648; Art ID: st-2015-s0641-l

Abstract Indium(III) chloride can be used as a cheaper alternative to gold(I) complexes as a catalyst in dehydrative reactions with allylic alcohols. There is often an improvement in yield and, in particular, indium(III) chloride outperforms gold(I) as a catalyst in chemoselective reactions. For example, substrates with pendent alkyne or alkene groups react poorly under gold(I) catalysis, but are better tolerated under indium(III) chloride catalysis.

Key words indium, gold, catalysis, allylic alcohols, allylation

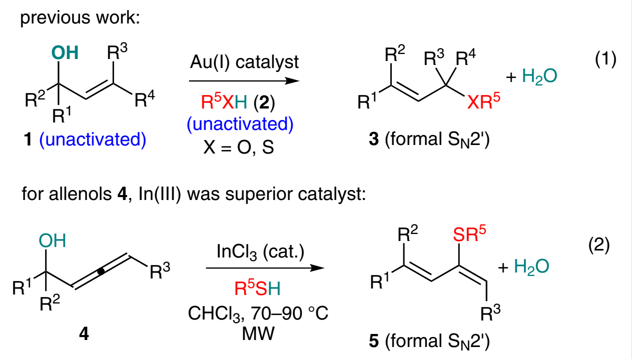
In recent years, additions of heteroatoms to C–C π-bonds have been greatly facilitated by developments in homogeneous gold(I) catalysis,[1] by virtue of the metal's excellent π-Lewis acidity.[2] More recently, gold-catalyzed dehydrative transformations of allylic alcohols **1** have emerged as mild and selective methods for allylations (Scheme 1, eq. 1).[3,4] Unlike many conventional transition-metal-based allylations, with a gold catalyst neither the allylic alcohol nor the incoming nucleophile need to be activated (the former with a leaving group or the latter with a base, for example); consequently, water is the sole byproduct. Within this context, we have recently developed gold-catalyzed intermolecular etherification (RXH = ROH)[5] and thioetherification (RXH = RSH)[6] reactions that are highly regioselective (formal S_N2'; Scheme 1, eq. 1). However, upon attempting to extend this chemistry to allenols **4**, we found that gold catalysis resulted in poor yields and/or regioselectivities, presumably because the diene products **5** are unstable in the presence of gold catalysts. Following a screen of other soft Lewis Acids, we discovered that indium(III) chloride is an excellent catalyst[7] for the dehydrative transformation shown in Scheme 1 (eq. 2).[8]

(from left to right) **Ai-Lan Lee** obtained her M.Sci. (Hons.) (2000) and her Ph.D. (2004) from the University of Cambridge, working under the supervision of Professor Steven V. Ley. She was subsequently awarded a Lindemann Trust Fellowship (2004–2005) to work at Boston College with Professor Amir H. Hoveyda on alkene metathesis. In 2006, Ai-Lan was appointed as a fixed-term lecturer at the University of Edinburgh, carrying out research with Professor David A. Leigh on rotaxane synthesis. She started as a lecturer at Heriot-Watt University in 2007, and was promoted to associate professor/reader in 2013. Her research interests include developing new gold- and palladium-catalyzed reactions and catalysts.

Graeme Barker Graeme obtained his M.Chem. (Hons.) in 2007 from the University of St Andrews and his Ph.D. in 2011 from the University of York, working under the supervision of Professor Peter O'Brien. He subsequently carried out research at the University of Sheffield as a postdoctoral research associate in the group of Professor Iain Coldham. He is currently a postdoctoral research associate in the Lee group at Heriot-Watt University, where his work focusses on enantioselective gold(I)-catalyzed reactions

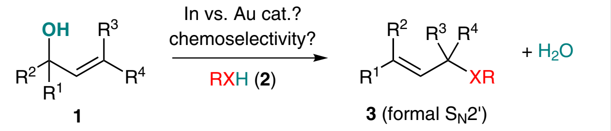
Louise Schaefer Louise received her M.Chem. (Hons.) in chemistry from Heriot-Watt University in June 2015. Her final-year masters research project was carried out under the supervision of Dr. Ai-Lan Lee and it focused on comparing indium(III) and Au(I) catalysis in the dehydrative reaction of allylic alcohols.

Stacey Webster Stacey graduated from Heriot-Watt University in 2013 with an M.Chem. (Hons.) degree in chemistry with industrial experience, having completed a yearlong placement at AstraZeneca. She is currently a second-year Ph.D. student in the Lee group at Heriot–Watt University, where her research is focused on the development of gold(I)- and indium(III)-catalyzed reactions.



Scheme 1

Since indium(III) chloride has several advantages, including a lower cost than gold(I) catalysts, a nontoxic nature, a lower heterophilicity (for example, it readily tolerates sulfur), and stability to air and water,[7b,e] we decided that it would be prudent to investigate the use of indium(III) chloride as an alternative catalyst in dehydrative reactions with allylic alcohols **1** (Scheme 2). We therefore set out to compare indium(III) chloride with gold(I) as a catalyst in these reactions,[9] in particular with substrates that were previously identified as being unreactive, low-yielding, or problematic during our initial studies with gold catalysis. For example, the excellent π-Lewis acidity of gold(I) means that pendent alkyne or alkene groups can be problematic in gold(I) catalysis, as they can often react to produce unwanted side products (see below).



Scheme 2

To this end, allylic alcohol **1a**, with an electron-rich aromatic substituent, was initially investigated (Table 1), as it produced a complex mixture of products under our previous general conditions.[5a] Note at this point that the choice of the gold catalyst was based on previous optimization studies: Gagosz's catalyst[10] ($Ph_3PAuNTf_2$) is the optimal catalyst for alcohol nucleophiles,[5a] and Echavarren's catalyst[11] **6** is the optimal catalyst with thiols.[12] Upon lowering the temperature and reducing the time (30 °C, 30–60 min), however, the reaction worked well with either indium(III) chloride or gold(I) catalysis. Indium(III) chloride produced better yields for both the alcohol nucleophiles **2a** and **2b** (77% vs. 67% for **2a**; 62% vs. 55% for **2b**; Table 1, entries 1–4, respectively) and for the thioacid nucleophile **2c** (85% vs. 78% for **2c**, entries 5 and 6). The difference in yield was more stark when *N*-(*tert*-butoxycarbonyl)-L-prolinol **2d**, which contains a proximal *N*-(*tert*-butoxycarbonyl) moiety, was used as the nucleophile: indium(III) chloride catalyzed the reaction to give an excellent 90% yield of **3ad**, whereas the gold(I) catalyst produced only a moderate 53% yield (entries 7 and 8, respectively). This difference is presumably due to the lower tolerance of the gold(I) catalyst toward the proximal *N*-(*tert*-butoxycarbonyl) moiety, as when this was situated further from the hydroxy group, as in substrate **2e**, both catalysts produced comparable yields (72% and 71%, respectively; entries 9 and 10). Unfortunately, when the lone pair on the nitrogen was more available (**2f** vs. **2d** and **2e**), neither indium(III) chloride nor gold(I) successfully catalyzed the reaction (entries 11 and 12), presumably due to deactivation of the catalyst.

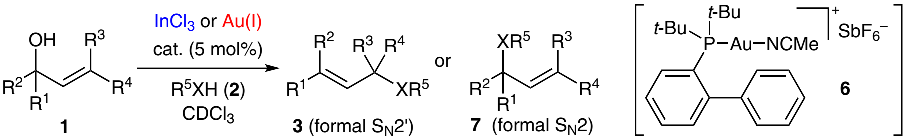
Since gold(I) is very alkynophilic,[13] our next aim was to probe the chemoselectivity by comparing the performance of indium(III) and gold(I) catalysts using nucleophile **2g**, which has a pendent alkyne group. Unsurprisingly, the reaction with gold(I) catalysis produced a complex mixture of products, presumably due to unwanted side reactions at the alkyne moiety (Table 1, entry 14). To our delight, however, the reaction with indium(III) chloride as the catalyst proceeded smoothly to give 79% of the desired product **3ag** (entry 13). This example shows that indium(III) chloride, unlike gold(I), is tolerant of pendent alkynes in the substrate.

Next, we examined the reaction of the tertiary allylic alcohol substrates **1b** with the thioacid **2c**, because the latter gave decent yields in its reactions with **1a** with indium(III) or gold(I) catalysis. Once again, the yield of the desired formal S_N2' product **3bc** was higher when indium(III) chloride was used as the catalyst (84% vs. 60%, Table 1, entries 15 and 16). On a larger 1 mmol scale, the yields improved to 97% and 82% respectively.[14]

Finally, we probed the chemoselectivity of the reaction by investigating morechallenging substrates: the allylic alcohols **1c**, **1d**, and **1e** with pendent alkene groups (Table 1, entries 17–22).[15] In all cases, indium(III) outperformed the gold(I) catalyst **6**. Allylic alcohol **1c** with a pendent monosubstituted alkene group, produced the desired product **3ch** in 48% yield (entry 17), whereas the corresponding gold(I)-catalyzed reaction gave a poor 15% of **3ch** together with a mixture of unidentified products (entry 18). The related allylic alcohol **1d** (commercially available linalool), with a pendent trisubstituted alkene group, also fared better under indium(III) catalysis. Although only a modest 31% isolated yield of **3dh** was obtained (entry 19), in comparison, gold(I) once again gave a mixture of unidentified products with only a poor 16% isolated yield of the desired **3dh** (entry 20). Finally, we investigated the reactions of commercially available geraniol (**1e**), the primary allylic alcohol isomer of **1d** (entries 21 and 22). A complex mixture of products was formed under gold catalysis, with only 9% of **3dh** isolated (entry 22). Interestingly, the formal S_N2 product **3dh** (which is the same as the formal S_N2' product from isomer **1d**; entry 19) was preferred, implying that the selectivity of these reactions is under thermodynamic control, as previously described.[6]

Since indium(III) chloride has been described as a soft Lewis acid,[16,17] the mechanism of the reaction is thought to be similar to that of the gold(I)-catalyzed reaction (Scheme 3).[5a,d,18] Activation of the alkene and H-bonding assisted delivery of the nucleophile (**I**), followed by elimination of the catalyst and water, also assisted by hydrogen bonding in **II**, produces the formal S_N2' product **3**.

Table 1 Comparison of Indium(III) and Gold(I) Catalysis



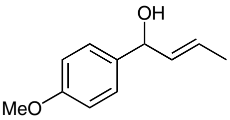
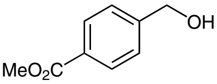
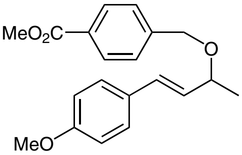
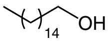
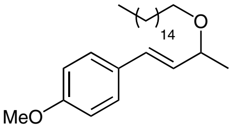
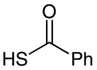
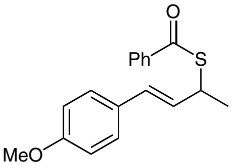
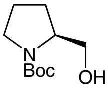
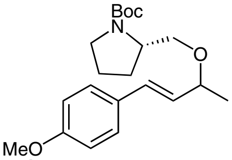
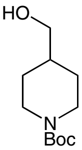
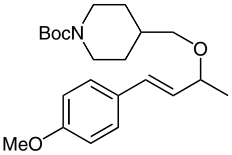
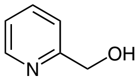
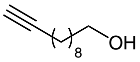
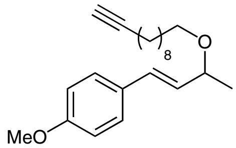
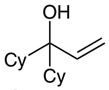
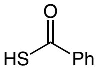
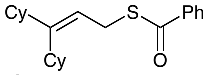
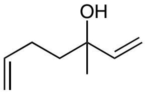
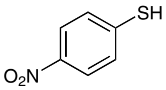
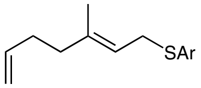
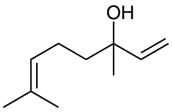
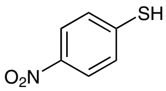
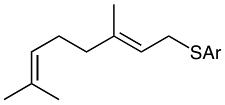
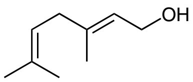
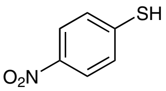
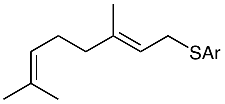
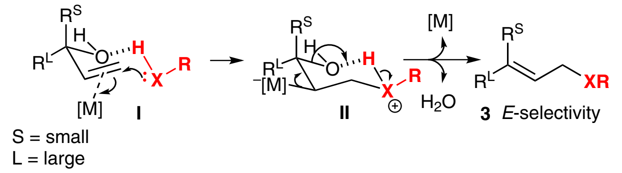
Entry	Allylic alcohol	Nucleophile[a]	Catalyst	Temp (°C)	Time (min)	Product	Yield[b] (%)	Ratio **3**/**7**	*E*/*Z*
1	 **1a**	 **2a**	In(III)	30	30	 **3aa**	77	>20:1	>20:1
2	**1a**	**2a**	Au(I)[c]	30	30	**3aa**	67	>20:1	>20:1
3	**1a**	 **2b**	In(III)	30	30	 **3ab**	62	>20:1	>20:1
4	**1a**	**2b**	Au(I)[c]	30	30	**3ab**	55	>20:1	>20:1
5	**1a**	 **2c**	In(III)	30	60	 **3ac**	85	>20:1	>20:1
6	**1a**	**2c**	Au(I)[d]	30	60	**3ac**	78	>20:1	>20:1
7	**1a**	 **2d**	In(III)	30	30	 **3ad**	90	>20:1	>20:1
8	**1a**	**2d**	Au(I)[c]	30	30	**3ad**	53	>20:1	>20:1
9	**1a**	 **2e**	In(III)	30	30	 **3ae**	72	>20:1	>20:1
10	**1a**	**2e**	Au(I)[c]	30	30	**3ae**	71	>20:1	>20:1

Table 1 (continued)

Entry	Allylic alcohol	Nucleophile[a]	Catalyst	Temp (°C)	Time (min)	Product	Yield[b] (%)	Ratio **3**/**7**	*E*/*Z*
11	**1a**	 **2f**	In(III)	30	30	no reaction	N/A	N/A	N/A
12	**1a**	**2f**	Au(I)[c]	30	30	no reaction	N/A	N/A	N/A
13	**1a**	 **2g**	In(III)	30	30	 **3ag**	79	>20:1	>20:1
14	**1a**	**2g**	Au(I)[c]	30	30	complex mixture	N/A	N/A	N/A
15	 **1b**	 **2e**	In(III)	50	60	 **3bc**	84 (97)[e]	>20:1	>20:1
16	**1b**	**2c**	Au(I)[d]	50	60	**3bc**	60 (82)[e]	>20:1	>20:1
17	 **1c**	 **2h**	In(III)	80	30	 **3ch** Ar = 4-$O_2NC_6H_4$	48 (**3ch**)	N/D[f]	3:1
18	**1c**	**2h**	Au(I)[d]	80	30	**3ch**[g]	15 (**3ch**)	N/D[f]	>20:1
19	 **1d**	 **2h**	In(III)	50	240	 **3dh** Ar = 4-$O_2NC_6H_4$	31 (**3dh**)	2.5:1	>20:1
20	**1d**	**2h**	Au(I)[d]	50	240	**3dh**[g]	16 (**3dh**)	2.5:1	>20:1
21	 **1e**	 **2h**	In(III)	50	240	 **3dh** (= **7eh**) Ar = 4-$O_2NC_6H_4$	28 (**3dh**)	3:1	>20:1
22	**1e**	**2h**	Au(I)[d]	50	240	**3dh**[g]	9 (**3dh**)	6:1	>20:1

[a] Alcohol nucleophiles: 5 equiv; thiol nucleophiles: 1.1 equiv (0.07 mmol scale based on **1**).
[b] Isolated yield.
[c] $Ph_3PAuNTf_2$.
[d] Catalyst **6**.
[e] 1 mmol scale, 2 h.
[f] Not determined, overlapping peaks.
[g] Together with a mixture of unidentified products.

The main advantage of indium(III) chloride is its greater tolerance of other C–C π bonds. In our previous work with allenols **4** (Scheme 1, eq. 2), control reactions showed that the diene products **5** reacted further under gold(I) catalysis, resulting in poor yields and complex mixtures. Similarly, the results presented in Table 1 show that pendent alkynes and alkenes are problematic under gold(I) catalysis as a result of unwanted side reactions, but pose less of a problem under indium(III) catalysis.



Scheme 3

In conclusion, indium(III) chloride can be used as a cheaper alternative catalyst to gold(I) in dehydrative reactions with allylic alcohols. Furthermore, among the substrates investigated, there was often an improvement in yield for indium(III) chloride catalysis in comparison with gold(I) catalysis; this improvement ranged from moderate to significant. In particular, indium(III) chloride outperformed gold(I) when *chemoselectivity* was an issue. For example, gold(I) gave a complex mixture of products from substrates containing pendent alkene or alkyne groups (for example, **1c** and **2g**), whereas indium(III) chloride successfully gave the desired products. Another situation in which indium(III) outperforms gold(I) as a catalyst is when the substrate contains proximal heteroatoms, as in the case of the nucleophile **2d**. We therefore hope that our studies will encourage others to consider indium(III) chloride as an alternative catalyst for dehydrative reactions with allylic alcohols, especially in situations where pendent C–C π-bonds are present.

Acknowledgment

We thank EPSRC (EP/K00736X/1) and Heriot-Watt University (James Watt Scholarship, S.W.) for funding. Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560648 and from the author.

References and Notes

(1) For selected reviews on homogeneous gold(I) catalysis, see: (a) Bandini, M. *Chem. Soc. Rev.* **2011**, *40*, 1358. (b) Bongers, N.; Krause, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 2178. (c) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910. (d) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (f) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (g) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896. (h) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (i) Li, Z. G.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (j) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (k) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448. (l) Sengupta, S.; Shi, X. *ChemCatChem* **2010**, *2*, 609. (m) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (n) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847.

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(14) **S-(3,3-Dicyclohexylprop-2-en-1-yl) Benzenecarbothioate (3bc); Typical Procedure**
A solution of allylic alcohol **1b** (221 mg, 1.0 mmol, 1 equiv) in CHCl$_3$ (1.0 mL) was added to a vial containing InCl$_3$ (10 mg, 5 mol%), thioacid **2c** (130 μL 1.1 mmol, 1.1 equiv), and CHCl$_3$ (8 mL). The solution was washed in with a further portion of CHCl$_3$ (1 mL), and the mixture was stirred at 50 °C for 2 h. Purification by column chromatography [silica gel, hexane–Et$_2$O (7:1)] gave a colorless oil; yield: 332 mg (97%, 0.969 mmol); R_f = 0.76 (hexane–Et$_2$O, 3:1). IR: 2922, 2849 (C–H), 1660 (C=O), 1596,

1581, 1447 (C–C Ar) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.98 (m, 2 H, Ar-H), 7.53–7.58 (m, 1 H, Ar-H), 7.41–7.46 (m, 2 H, Ar-H), 5.27 (t, *J* = 8.1 Hz, 1 H, C=C*H*CH_2), 3.81 (d, *J* = 8.1 Hz, 2 H, C=CHC*H*$_2$), 2.45–2.54 (m, 1 H, alkyl-H), 1.87–1.85 (m, 1 H, alkyl-H), 1.50–1.80 (m, 10 H, alkyl-H), 1.08–1.40 (m, 10 H, alkyl-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 192.5 (C), 155.7 (C), 137.4 (C), 133.3 (CH), 128.7 (CH), 127.3 (CH), 116.0 (CH), 41.1 (CH), 40.7 (CH), 34.9 (CH_2), 31.1 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 26.7 (CH_2), 26.4 (CH_2), 26.3 (CH_2). HRMS (APCI): *m/z* [M + H]$^+$ calcd for $C_{22}H_{31}OS$: 343.2090; found: 343.2087.

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(18) See ref. 5a for control experiments proving that the reaction is not catalyzed by Brønsted acid, and ref. 5d for detailed mechanistic investigations.