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Intermolecular Mono- and Dihydroamination of Activated Alkenes Using a Recoverable Gold Catalyst

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A combination of gold chloride organometallic complex and a silver salt was used to catalyze intermolecular hydroamination of activated alkenes, i.e aza-Michael reactions. The gold-catalyzed reactions of activated alkenes with nitrogen substrates were investigated and found to afford various mono- and dihydroamination products, the latter being rare and original. After flash chromatography, gold NHC catalyst could be recovered as a gold hydroxide NHC complex. When combined with a silver salt, the gold complex lead again to an active hydroamination catalyst.

Introduction

Catalysis offers highly selective and atom-economic reactions but challenges remain for some reactions like the synthesis of amines through hydroamination reactions.[1] Recently, group 11 metals have been highlighted by various contributions in the field. Silver was recently shown to be active for hydroamination of alkenes and dienes.[2] Copper was successfully used for diamination,[3] carboamination[4] and hydroamination[5] reactions. The usefulness of gold[6] was pointed out using alkyne[1,6,7] alkene,[3,8,10e,10i] allene[9] and diene[2,10] substrates for both intra- and intermolecular hydroamination reactions as well as for diaminations. Mechanistic investigations into gold-catalyzed hydroamination reactions by He et al., and later by Togni et al., have demonstrated that gold precursor was the main catalyst; no Brønsted acid was generated by reaction of cationic gold complexes with amine reagents.[11] Interestingly, Ujaque et al. have compared, by calculations, the mechanisms of acid- and gold-catalyzed hydroamination of alkenes and dienes.[12] Whereas the acid-catalyzed process was shown to be concerted, the gold-catalyzed reaction was found to be stepwise for two envisioned pathways, the nucleophile-assisted and counterion-assisted pathways. Indeed, a proton-transfer agent, i.e the nucleophile or the counterion, was crucial to the lowering of the energy barrier for the proton transfer reaction. Toste, Goddard et al. studied, using calculations and experiments, the intramolecular aminoauration of unactivated alkenes providing evidence of an *anti*-addition mechanism for alkene aminoauration.[13] However, once prepared, such putative catalytic intermediates did not allow the hydroamination reaction to proceed affording only starting alkenes. The authors concluded this was due to the high energy barrier calculated for protodeauration.[13] Finally, the mechanism of gold-catalyzed asymmetric intramolecular hydroamination/hydroalkoxylation of allenes was recently investigated by Nguyen et al. using a chiral phosphate counterion. The latter was shown to act as a ligand phosphate counterion was shown to act as a ligand for the gold species during all reactions.[14] These, and other findings, support the idea that achieving a deep understanding of gold catalyst activity in hydroamination reactions remains a challenging endeavor.

Following our interest in Cu^{I} and Cu^{II} catalysts for inter- and intramolecular hydroamination of unactivated alkenes,[5g] we recently focused our attention on intermolecular hydroamination of activated alkenes. Though the aza-Michael reaction has been largely studied before,[15] organometallic gold catalysts were, to the best of our knowledge, never applied to this particular reaction. Herein, we report on the advantages, scope and limits of gold catalysts in aza-Michael reactions. The scope of reactivity for these catalysts is limited to mono- and original dihydroamination reactions. Results are highlighted by mechanistic investigations focusing on the role of additives, the synthesis of potent intermediates, and on kinetic studies.

Results and Discussion

We initially studied various Au^{I} and Au^{III} catalysts for the addition of benzamide **2** to cyclohexenone **1** (Table 1).

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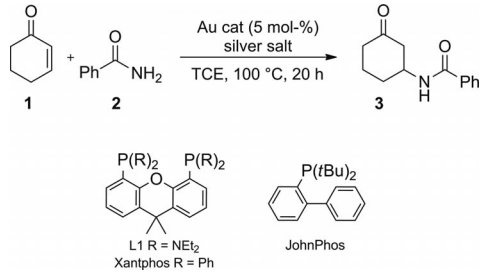
First, we showed IPrAuCl was not catalysing the reaction by itself and, instead, needed to react with AgOTf to afford the active catalyst IPrAuOTf[16] (Table 1, Entry 2 vs. 3). Conversions into **3** were higher using Au^I catalyst with electron-rich phosphane (Table 1, Entries 7 vs. 1) or NHC ligands (Table 1, Entries 4 and 2). The use of IAd ligand (Table 1, Entry 5) revealed the reaction limits with regards to steric hindrance when a NHC ligand was used. Moreover, the use of an additional benzotriazole ligand for Au^I[17a] reduced conversion into **3** (Table 1, Entry 6 vs. 2). Tricoordinated Au^I catalysts[17b,17c] combined with AgOTf were active when TCE was used as a solvent (Table 1, Entries 8 and 9) whereas the use of toluene significantly decreased conversion into **3** probably due to disproportionation of catalysts into other complexes.

Table 1. Screening of various gold complexes.

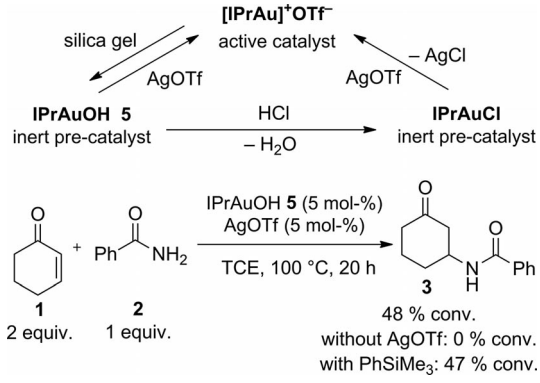


Entry	Catalyst[a,b]	Silver salt	Conv. of **3** (%)[c]
1	PPh_3AuCl	AgOTf (5 mol-%)	23
2[d]	IPrAuCl	AgOTf (5 mol-%)	52
3	IPrAuCl	–	0
4	I*t*BuAuCl	AgOTf (5 mol-%)	65
5	IAdAuCl	AgOTf (5 mol-%)	28
6[e]	IPrAu[BtH]OTf	–	27
7	JohnPhosAuCl	AgOTf (5 mol-%)	57
8	L1AuCl	AgOTf (5 mol-%)	13 (0[f])
9	XantphosAuCl	AgOTf (5 mol-%)	50 (20[f])
10	$IPrAuCl_3$	AgOTf (5 mol-%)	36
11	$IPrAuCl_3$	AgOTf (10 mol-%)	36
12	$IPrAuCl_3$	AgOTf (15 mol-%)	18

[a] Reactions performed in TCE (1,1′,2,2′-tetrachloroethane) unless otherwise stated, with 2 equiv. of **1** and 1 equiv. of **2** (0.5 mmol) using 5 mol-% of gold catalyst and 5 mol-% of AgOTf. [b] IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, I*t*Bu = 1,3-di-*tert*-butylimidazol-2-ylidene, IAd = 1,3-bis(1-adamantyl)imidazol-2-ylidene, JohnPhos = 2-(di-*tert*-butylphosphanyl)biphenyl, L1 = P,P′-(9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis[*N*,*N*,*N*′,*N*′-tetraethylphosphonous diamide], Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene. [c] Measured by GC. [d] Same result if 1 equiv. $PhSi(Me)_3$ was added. [e] BtH for benzotriazol.[16] [f] Performed in toluene.

Finally, cationic Au^{III} catalysts proved to be less active regardless of the amount of silver salts used (Table 1, Entries 10–12). No change in conversion was noticed whether in-situ or ex-situ Au catalyst synthesis was employed. Moreover, conversion into **3** remained unchanged upon filtration through Celite™ of the IPrAuOTf species;[16] no "silver effect" on gold catalyst could be observed.[17d] It was worth noting that no Brønsted acid species was formed during the reaction since the completeness of conversion remained unchanged when one equivalent of $PhSiMe_3$ was used as a proton trap (Table 1, Entry 2). The results obtained herein using IPrAuOTf catalyst required reactions to be run for 20 hours and at 100 °C. Relative to previously reported catalysts which allowed the synthesis of **3**[15c,f] and other compounds[15] at room temp. or below, IPrAuOTf was not an active catalyst. By contrast, AuCl and $AuCl_3{\cdot}3H_2O$ were reported to be active catalysts for aza-Michael reactions at room temperature within few hours.[15a]

We were particularly pleased to recover our Au^I catalyst. Indeed, using a simple flash chromatography on silica gel for the purification of a crude reaction mixture with EtOAc and petroleum ether solvents, we isolated aza-Michael product **3** and a gold complex. The latter was identified as IPrAuOH **5** and could be easily converted back into IPrAuCl by reaction with HCl. On the whole, this constitutes a new synthetic pathway for the preparation of a useful reagent like **5**[18c,18d,18e] from cationic $NHCAu^I$ complex. Interestingly enough, when **5** was combined with an equimolar amount of AgOTf, the reaction of benzamide **2** with cyclohexenone **1** was catalyzed again, affording **3** in a 48% conversion (Scheme 1).

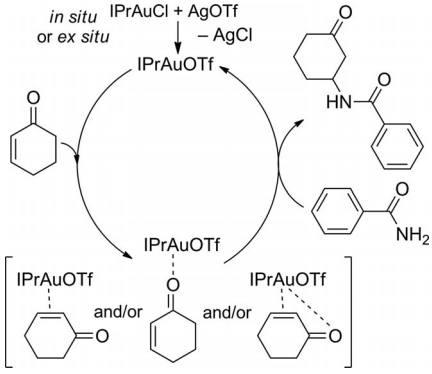


Scheme 1. IPrAuOH **5** as a recovered and useful pre-catalyst.

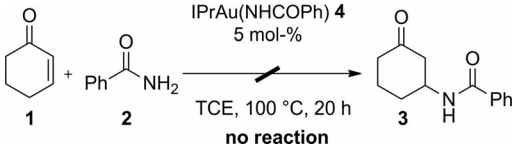
It is worth noting that no Brønsted acid species could be identified during aza-Michael reactions; 47% conversion was obtained when one equivalent of $PhSiMe_3$ was used as a proton trap. Such a result was quite close to the 52% conversion obtained using IPrAuOTf catalyst and demonstrates the usefulness of the combination of Ag^I salts with Au^I hydroxy complexes to form catalytically active cationic Au^I complex. Moreover, the reaction conversion into **3** remained unchanged upon removal of AgCl by filtration through Celite™ of the IPrAuOTf species. Hence, no "silver effect" on the gold catalyst was observed.[17d] By way of proof, IPrAuOH **5** was allowed to react first with $AgBF_4$ and latter with pyridine to afford already known complex $[IPrAu(pyridine)]^+BF_4^-$ **6**[19] in 86% yield.

A probable mechanism for the IPrAuOTf-catalyzed reaction of **1** and **2** is highlighted in Scheme 2. Whereas the π-philic Lewis acidity of gold complexes to C–C multiple bonds has been extensively studied,[6,8] the oxophilic Lewis acidity of gold species has only recently been supported.[20] Hence, coordination of IPrAuOTf to **1** can lead to three possible intermediates which further react with amide **2** to

afford product **3** (Scheme 2). Despite efforts to identify such intermediates, ^{13}C NMR analyses failed to reveal any evidence of Au^I enone activation. The chemical shift of the keto group was not seen, regardless of relaxation or acquisition times used. Moreover, to determine whether the benzamide reagent was activated by the Au^I catalyst or not, related amido IPrAu^I complex **4** was prepared.[18a,18b] No reaction was observed when **4** was subjected to the mixture of **1** and **2** (Scheme 3). In addition, we recalled that Au^I catalysts are not likely to generate Brønsted–acid by reaction with amine reagents. Therefore, Au^I catalysts seemed only to activate the alkene substrate, thus allowing reaction of the resulting incipient carbocation with the amine nucleophile.[11]



Scheme 2. Probable mechanism for IPrAuOTf-catalyzed reaction of **1** and **2**.

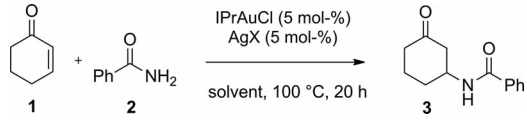


Scheme 3. IPrAu(NHCOPh) **4** as catalyst for the reaction of **1** and **2**.

We next focused our attention on the influence of the reaction parameters by varying the solvent, anion, and amount of alkene **1** allowed to react with nucleophile **2** (Table 2). No significant solvent-dependent differences were noted. Toluene proved to be useful in a fashion similar to 1,1′,2,2′-tetrachloroethane (TCE) or dioxane. DME was less effective (Table 2, Entries 1, 10–12). Among the various anions tested, triflate and hexafluoroantimonate anions appeared to be most appropriate (Table 2, Entries 1, 5–9). Finally, allowing an excess of alkene **1** to react with amine **2** drastically improved conversions from 28 up to 91% for ten equivalents of **1** (Table 2, Entries 1–4). Such a reactivity enhancement has been previously noted for several catalytic hydroamination reactions of unactivated alkenes.[1c,1d,8e]

Regarding the catalytic activity of Ag^I species for hydroamination of alkenes and dienes,[2] we examined the potential of various Ag^I salts to catalyze the reaction of activated alkenes with amines. On the whole, the Ag^I-catalyzed reactions of benzamide **2** and cyclohexenone **1** lead to product **3**

Table 2. Screening of reaction conditions.

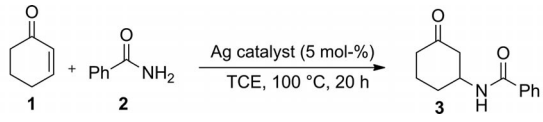


Entry[a]	Solvent	AgX	Alkene (equiv.)	Conv. (%)[b]
1	TCE	AgOTf	1	28
2	TCE	AgOTf	2	52
3	TCE	AgOTf	5	83
4	TCE	AgOTf	10	91
5	TCE	$AgSbF_6$	1	33
6	TCE	AgPNB	1	0
7	TCE	$LiNTf_2$	2	0
8	TCE	$AgNTf_2$	1	13
9	TCE	$AgBF_4$	1	14
10	toluene	AgOTf	1	36
11	dioxane	AgOTf	1	25
12	DME	AgOTf	1	18[c]

[a] Reactions performed with 1 equiv. or more of **1** and 1 equiv. of **2** (0.5 mmol) using 5 mol-% of IPrAuCl and 5 mol-% of AgX. [b] Measured by GC. [c] Performed at reflux (e.g., 85 °C).

in lower conversions than those achieved with Au^I catalysts (Table 3, Entries 1–5). The use of an additional ligand did not enhance the conversion (Table 3, Entries 6–10).

Table 3. Screening of various silver salts.

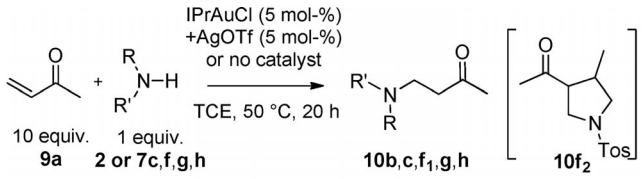


Entry	Catalyst[a]	Additive[b]	Conv. (%)[c]
1[d]	AgOTf	IPrAuCl	52
2	AgOTf	–	42
3	$AgSbF_6$	–	44
4	Ag_2O	–	0
5	AgO_2CPh	–	0
6[d]	Ag_2O	IPr·HCl	0
7[d]	Ag_2O + $AgSbF_6$	IPr·HCl	7
8	$AgSbF_6$	$P(OPh)_3$	31
9[d]	$AgSbF_6$	$P(OPh)_3$	22
10[d]	$AgSbF_6$	$P(Ph)_3$	0

[a] Reactions performed with 2 equiv. of **1** and 1 equiv. (0.5 mmol) of **2** using 5 mol-% of Ag^I salt. [b] 5 mol-% additive. [c] Conversion measured by GC. [d] A pre-formed catalyst was used.

Next, in order to explore the scope of substrates for these Au^I-catalyzed hydroamination reactions, several weak nucleophiles were allowed to react with 10 equiv. of methyl vinyl ketone **9a** in the presence of Au^I catalyst (Table 4). Although reactions of amines **2** or **7h** needed heatings at 100 °C to react (Table 4, Entries 1 and 5), other reactions proceeded well at 50 °C affording compounds **10c**,**f**$_1$,**g** in good yields (Table 4, Entries 2–4). At 50 °C, the catalyzed reaction of **9a** with *N*-tosylallylamine **7f** was shown to follow a first order kinetic rate law (see Supporting Information, Figure S1). Moreover, no evidence for any intramolecular hydroalkylation reaction between the alpha ketone and the *N*-allyl functional group could be found.[21]

Table 4. Amine reactivity towards methyl vinyl ketone **9a**.



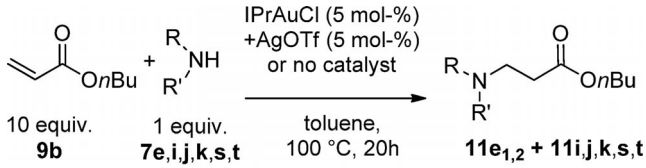
Entry	Amine	Yield (%)[a]	Conversion (%) without catalyst[b]
1[c]	**2**	87	0
2	**7c**	95	0
3	**7f**	84[d]	0
4	**7g**	90	0
5[e]	**7h**	77	70

[a] Isolated yield. [b] Performed at 100 °C for 20 h; conversions measured by ^{1}H NMR spectroscopy. [c] Performed at 100 °C. [d] When at 100 °C in toluene, 65% of **10f$_1$** and 32% of **10f$_2$**. [e] Performed in toluene at 100 °C for 40 h.

The reaction carried out at 100 °C afforded some hydroalkylated product **10f$_2$** (Table 4, Entry 3). When no catalyst was used, reaction of **9a** proceeded only with amine **7h** most likely because of **7h** higher nucleophilicity (Table 4, Entry 5). Though not always addressed, literature reports of such uncatalyzed "background" reactions relative to aza-Michael additions are known.[5c,22,23] By comparing reactivity and pK_a values in DMSO of the amine reagents involved, we found that imine **7h** (pK_a 31.0) was the strongest nucleophile of the series and gave a lower yield than oxazolidone **7c** (pK_a 20.8) or other amines in the catalytic reactions. Hence, we envisioned that nucleophile reactivity depends, to some extent, on potential steric hindrance around the nitrogen atom.

We studied the reactivity of butyl acrylate **9b** with some secondary amines at 100 °C (Table 5). With the exception of amine **7e** which gave isomers **11e$_1$** and **11e$_2$**[24] in poor yields (Table 5, Entry 1), the uncatalyzed reactions proceeded at 100 °C with efficiencies being on par with the Au^I-catalyzed ones, the latter allowing most amines to react (Table 5, Entries 2–4). The fact that no conversion was obtained for *N*-methylaniline and diisopropylamine (Table 5, Entries 5 and 6) supports the notion that less hindered amines are more effective reagents in hydroamination reaction than the sterically hindered ones. The scope of useful alkenes for these Au^I-catalyzed hydroamination reactions proved to be rather modest; terminal enones were the most active substrates (see Supporting Information, Tables S1 and S2). In general, the poor activity of IPrAuOTf contrasts with previously reported catalysts that facilitate the addition of amides, carbamates and other nucleophiles upon various activated alkenes at room temperature.[15]

Table 5. Secondary amines reactivity towards butyl acrylate **9b**.

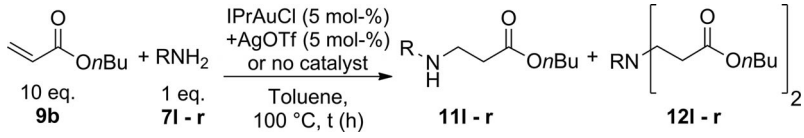


Entry	Amine	Yield (%)[a]	Yield (%) at 100 °C with no catalyst[a]	Yield (%) at 30 °C with no catalyst[a,b]
1[c]	**7e**	88	15 (6+9)[f]	<5[g]
2[c,d]	**7i**	86	70	<5[g]
3[c]	**7j** (nBu)$_2$NH	90	86	15
4	**7k** MeBnNH	96	100	55
5	**7s** MePhNH	0	0	0
6	**7t** (iPr)$_2$NH	0	0	0

[a] Isolated yields. [b] 20 h reaction. [c] TCE as solvent. [d] 23 h reaction. [e] 26 h reaction. [f] Compounds **11e$_1$** and **11e$_2$**. [g] Measured by ^{1}H NMR spectroscopy.

The reactivity of primary amines **7l–r** towards butyl acrylate **9b** was studied and found to reveal interesting features (Table 6). Using Au^I catalyst, reactions with amines **7l–r** lead to some monohydroamination products **11l–r**, but predominantly afforded dihydroamination products **12l–r**. Strikingly, use of amines **7o** and **7q** led selectively to monohydroamination products **11o** and **11q** (Table 6, Entries 4 and 6) whereas reactions with amine **7p** and hydrazine **7r** afforded single dihydroamination products **12p** and **12r** in high yields (Table 6, Entries 5 and 7). Consequently, we postulated that sterically bulky primary amine reagents favored the synthesis of monohydroamination products whereas less hindered amines mainly led to dihydroamination products. Such a trend was also confirmed by reactions carried out at 100 °C in the absence of catalyst; these reactions afforded compounds **11l–r** and/or **12l–r**, except for the reaction involving amine **7o** (Table 6, Entry 4). Reactions using no catalyst were found to lack the previously noted selectivity for dihydroamination products (Table 6, Entries 1–3). Moreover, lowering the temperature to 30 °C induced selective formation of compounds **11l–n,p** (Table 6,

Table 6. Butyl acrylate **9b** reactivity towards various primary amines.



Entry	Amine **7l–r**	Time [h]	Yield (%)[a] [**11** + **12**]	Yield (%)[a] at 100 °C without catalyst [**11** + **12**]	Yield (%)[a,b] at 30 °C without catalyst [**11** + **12**]
1	**7l** *i*PrNH$_2$	40	70 [0 + 70]	75 [37 + 38][c]	8 [8 + 0]
2	**7m** BnNH$_2$	20	99 [17 + 82]	100 [53 + 47][d]	25 [25 + 0][d]
3	**7n** CyNH$_2$	30	99 [39 + 60]	100 [100 + 0]	23 [23 + 0]
4	**7o** PhNH$_2$	70	65 [65 + 0]	0	–
5	**7p** *n*BuNH$_2$	20	97 [0 + 97]	90 [0 + 90]	44 [44 + 0]
6	**7q** *t*BuNH$_2$	20	28 [28 + 0]	32 [32 + 0]	0
7	**7r** BzNHNH$_2$	20	100 [0 + 100]	100 [0 + 100]	5 [0 + 5]

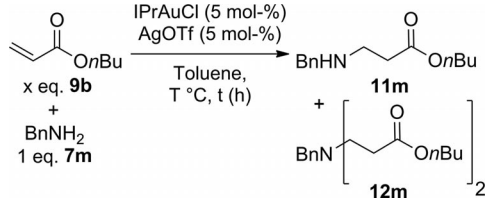
[a] Isolated yield; all reactions performed with 0.5 mmol of amine. [b] 20 h reactions. [c] 40 h reactions. [d] Performed with 5 equiv. of alkene.

Entries 1–3, 5). As a general trend, whenever the di-addition product was obtained, a higher selectivity was obtained by using a cationic Au^{I} catalyst. To the best of our knowledge, such results are rare examples of dihydroamination reactions with or without the use of an Au^{I} catalyst.[25] Interestingly, mono- and dihydroarylation reactions between electron-rich arenes and activated alkenes were previously reported by Hashmi et al. using an Au^{III} catalyst.[26]

To deepen our knowledge of the synthesis of these mono- and dihydroamination products, we studied Au^{I}-catalyzed reaction of amine **7m** with alkene **9b** by changing reaction condition variables one at a time (Table 7). By using a single equivalent of reagent **9b**, monohydroamination product **11m** was formed preferentially over **12m** in 5 hours. An increase of the reaction time implied minor changes in the ratio of the two products (Table 7, Entries 2 and 3). The use of 5 equiv. of alkene **9b** improved the yield of dihydroamination product **12m**; which could be drastically enhanced by switching the reaction time from 5 to 10 hours (Table 7, Entries 1, 4, 5). Decreasing reaction temperature favoured synthesis of **11m** over **12m** despite the use of 5 equiv. of alkene **9c** (Table 7, Entries 7–15). At 60 °C, compound **11m** was obtained selectively in high yield without the use of any catalyst (Table 7, Entry 10 vs. 1, 11) whereas the same reaction outcome was reached at only 40 °C with the use of either Au^{I} or Ag^{I} catalysts (Table 7, Entries 12 and 13). In addition, reaction of amine **7m** with alkene **9b** proved to be sensitive to the nature of the solvent used; the neat reaction proceeded extremely well. It was worth noting that addition of water to the reaction medium significantly increased yields of **11m** (Tables S3 and S4 of Supporting Information). Such rate enhancements in aza-Michael reactions have been previously observed when using various additives.[27]

In an attempt to see if reaction of amine **7m** and alkene **9b** would be autocatalytic,[28] we allowed monohydroamination product **11m** to catalyze the reaction of **7m** and **9b**. The reaction using 10 mol-% of **11m** as catalyst afforded a lower yield of **11m** relative to the reaction run without catalyst (Scheme 4); no autocatalysis from **11m** could be supported.

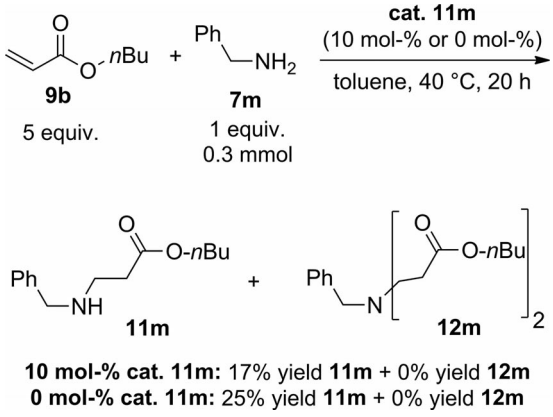
Table 7. Reaction of butyl acrylate **9b** and benzylamine **7m**; selectivity change depending variation of conditions.



Entry	Temp. [°C]	Time [h]	Alkene (equiv.)	Yield (%)[a] [**11m** + **12m**]
1[b]	100	20	5	100 [53 + 47]
2	100	5	1	84 [81 + 3]
3	100	10	1	94 [85 + 9]
4	100	5	5	100 [61 + 39]
5	100	10	5	94 [20 + 74]
6	100	20	5	96 [23 + 73]
7	80	20	5	97 [48 + 49]
8	60	20	5	100 [86 + 14]
9[c]	60	20	5	100 [79 + 21]
10[b]	60	20	5	86 [86 + 0]
11[b]	40	20	5	25 [25 + 0]
12[c]	40	20	5	83 [83 + 0]
13[d]	40	20	5	98 [98 + 0]
14[e]	0	20	2	40 [40 + 0]
15[e,f]	0	20	2	15 [15 + 0]

[a] Isolated yield. [b] Performed without gold(I) and silver(I) catalysts. [c] Catalyst was synthesized prior to use (room temp., 2 h). [d] Performed with only AgOTf. [e] Performed in CH_2Cl_2. [f] Performed with no Au^{I} and Ag^{I} catalysts at 0.2 mmol scale for BnNH$_2$.

To gain more insight into these mono- and dihydroamination reactions, we performed a kinetic study on the reaction of **7m** and **9b** without any catalyst. First, that reaction was performed at 23 °C and the plot of yields vs. time revealed that the maximum yield of monohydroamination product **11m** was reached after 2000 minutes (Figure 1). Af-



Scheme 4. Reaction between **9b** and **7m** for probing autocatalysis by **11m**.

ter this point in time curves showed conversion of **11m** into dihydroamination product **12m** by reacting again with alkene **9b** to afford a 20% yield of **12m** in 3600 minutes (see Figure 1). However, after reaching a 65% value, conversion of **11m** into **12m** remained at a plateau for a long time, most likely due to an equilibrium for the second addition between the aza-Michael reaction and its retro-reaction (see Supporting Information, Figure S2).[29]

The plot of $\ln(n_{amine}$ **7m**$)$ vs. time (min) for about three half-lives (one half-life being 990 min) gave a linear curve which could be fitted with a first-order kinetic law (R^2 = 0.9938) by use of the linear least-squares technique. Such a rate law could be expected as long as ten equivalents of alkene were used with respect to the amine (Figure 1). Next, another kinetic study was performed on the reaction of **7m** and **9b** at 23 °C using IPrAuOTf as catalyst. As shown by the plot of yields vs. time, reaction was noticeably accelerated relative to the previous run without any catalyst. Indeed, an 80% maximum yield of monohydroamination product **11m** was reached after 500 minutes (Figure 2). After that point, a clear linear conversion of **11m** into **12m** could be seen by reaction with **9b**. Indeed, dihydroamination was significantly accelerated by the use of Au^I catalyst with a 20% yield of **12m** reached in 900 minutes (Figure 2). Moreover, the previously observed retro–aza–Michael reaction was prevented by the use of Au^I catalyst as long as a linear conversion of **11m** into **12m** could be seen along time.

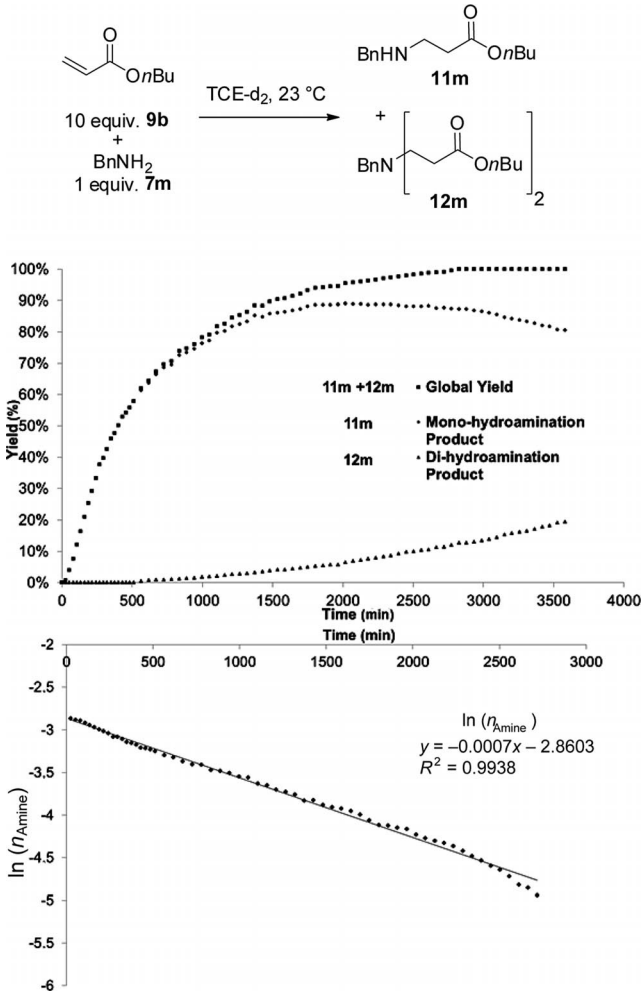


Figure 1. Kinetic profiles for the uncatalyzed reaction of **9b** with **7m** at 23 °C in TCE-d_2.

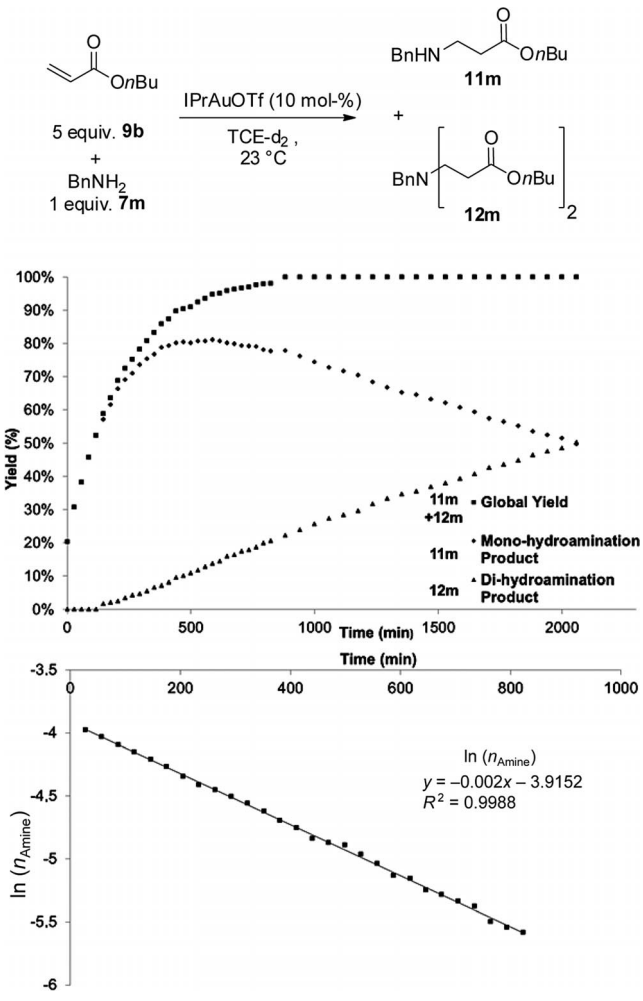


Figure 2. Kinetic profiles for the reaction of **9b** with **7m** at 23 °C in TCE-d_2 catalyzed by 10 mol-% of IPrAuOTf.

The plot of ln(n_{amine} **7m**) vs. time (min) for about two half-lives (one half-life being 347 min) gave a linear curve which could be fitted with a first-order kinetic law (R^2 = 0.9988) by use of the linear least-squares technique. Again, the use of ten equivalents of alkene with respect to the amine logically implied such a rate law (Figure 2).

A last kinetic study was performed on the uncatalyzed reaction of mono-hydroamination product **11m** and alkene **9b** at 100 °C. A maximum yield of 70% in dihydroamination product **12m** was quickly obtained in 500 min. The resulting kinetic curve was fitted with a first–order kinetic law in a way similar to that used for the IPrAuOTf-catalyzed reaction of alkene **9a** with tosyl allylamine **7f** (see Supporting Information, Figures S1 and S3).

Conclusions

The gold-catalyzed addition of amines to various activated alkenes was investigated and found to produce monohydroamination and dihydroamination products. By requiring a 100 °C heating, IPrAuOTf catalyst proved to be a less active catalyst for aza-Michael reactions relative to previously reported metal catalysts which allowed reactions to proceed primarily at room temperature or below. However, the IPrAuOTf catalyst could be recovered as IPrAuOH, an inert gold hydroxide complex which lead again to active IPrAuOTf catalyst when combined with silver triflate. Moreover, the double–addition of an amine on two equivalents of alkene, i.e. dihydroamination reaction, was favored using the Au^I catalyst and led to rare and original examples of dihydroamination products. Steric hindrance of the amine was shown to control selectivity of mono- and dihydroamination reactions. Further investigations will be reported in due course.

Experimental Section

General Remarks: All solvents were dried using standard methods. Alkenes were distilled under vacuum over CaH_2 and stored over molecular sieves (4 Å). Amine substrates were placed under vacuum during one hour before use, or distilled from CaH_2 if they were liquid. All silver salts, gold salts and ligands were weighed inside a glovebox. All reactions were carried out under a dry nitrogen atmosphere. Analytical thin layer chromatography (TLC) was performed on Merck pre-coated 0.20 mm silica gel Alugram Sil 60 G/UV_{254} plates. Flash chromatography was carried out with Macherey silica gel 60 M. ^1H (300 MHz or 400 MHz), ^{13}C (75 MHz) and ^{31}P (121 MHz) NMR spectra were acquired with Bruker Avance spectrometers. Chemical shifts are reported downfield of Me_4Si and coupling constants are expressed in Hz. 1,3,5-trimethoxybenzene and 1,2,4,5-tetrachlorobenzene were used as internal standards when needed. Gas chromatography analyses were done with GC Varian 3900 and 430 using Alltech EconoCap EC-5™ column (30 m, 0.25 mm, 0.25 µm) with program (5 °C/min, 100–230 °C, 36 min.) and with tetradecane as internal standard. GC–MS analyses were performed on a Shimadzu QP2010+ using Supelco column SLB™-5 ms (30 m, 0.25 mm, 0.25 µm). Infrared spectra were recorded using a ThermoScientific-Nicolet 6700 spectrometer; the samples being prepared with KBr powder. HRMS-ESI analyses were performed at CUMA-University Lille Nord de-France. Elemental analyses were performed with an Elementar Vario Micro Cube apparatus at UCCS, University Lille Nord de France. See Supporting Information for other details.

General Procedure for Catalysis Conditions Screening: IPrAuCl (0.025 mmol, 15.5 mg) was dried during 30 min under vacuum and then AgOTf (0.025 mmol, 6.4 mg) was added (in a glovebox). Next, dry toluene (1 mL), and freshly distilled benzylamine (0.5 mmol, 55 µL) were added under a nitrogen atmosphere. After stirring at the corresponding time and temperature, the mixture was concentrated under vacuum, and the resulting product was isolated by flash chromatography.

General Procedure for Activated Alkene Screening: IPrAuCl (0.025 mmol, 15.5 mg), benzotriazole (0.5 mmol, 59.6 mg) and activated alkene (5.0 mmol) (if solid) were added in a Schlenk flask. These solids were dried during 30 min under vacuum and AgOTf (0.025 mmol, 6.4 mg) was added (in a glovebox). Then, dry 1,1′,2,2′-tetrachloroethane (1 mL), and activated alkene (5.0 mmol) (if liquid) were added under a nitrogen atmosphere. After stirring at 100 °C for the corresponding time, the mixture was concentrated under vacuum, and the corresponding product was isolated by flash chromatography.

General Procedure for Amine Substrate Screening: IPrAuCl (0.025 mmol, 15.5 mg), and amine substrate (0.5 mmol) (if solid) were added in a Schlenk flask. These solids were dried during 30 min under vacuum and AgOTf (0.025 mmol, 6.4 mg) was added (in a glovebox). Then, dry toluene (1 mL), butyl acrylate (5.0 mmol, 0.7 mL), and freshly distilled amine substrate (0.5 mmol) (if liquid) were added under a nitrogen atmosphere. After stirring at 100 °C for the corresponding time, the mixture was concentrated under vacuum, and the resulting product was isolated by flash chromatography.

General Procedure for Amine Reactivity Screening with Methyl Vinyl Ketone: IPrAuCl (0.025 mmol, 15.5 mg) and amine substrate (0.5 mmol) (if solid) were added in a Schlenk flask and dried under vacuum for 30 min. Next, in a glovebox, AgOTf (0.025 mmol, 6.4 mg) was added followed by dry 1,1′,2,2′-tetrachloroethane (1 mL), methyl vinyl ketone (5.0 mmol, 0.4 mL), and amine substrate (0.5 mmol) (if liquid). After stirring at 50 °C at the corresponding time, the mixture was concentrated under vacuum, and the resulting product was isolated by flash chromatography.

Butyl 3-(Dibutylamino)propanoate (11j): Isolated after flash chromatography with petroleum ether/NEt_3 (9:1), as a colourless oil (0.45 mmol, 116 mg, 90% yield). ^1H NMR (300 MHz, $CDCl_3$,): δ = 0.85–0.95 (q*, 9 H), 1.20–1.45 (m, 10 H), 1.58 [quin, J(H,H) = 7.2 Hz, 2 H], 2.30–2.45 (m, 6 H), 2.75 [t, J(H,H) = 7.5 Hz, 2 H], 4.05 [t, J(H,H) = 6.7 Hz, 2 H] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_3), 14.1 (2 CH_3), 19.1 (CH_2), 20.6 (2 CH_2), 29.3 (2 CH_2), 30.7 (CH_2), 32.4 (CH_2), 49.4 (CH_2), 53.6 (2 CH_2), 64.2 (CH_2), 173.1 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2959, 2933, 2873, 1717, 1202 cm^{-1}. HRMS (ESI) m/z calcd. for $C_{15}H_{32}NO_2$: 258.2428 [M + H]$^+$, found 258.2423.

Butyl 3-[Benzyl(methyl)amino]propanoate (11k): Isolated after flash chromatography with petroleum ether/ethyl acetate/NEt_3 (9:1:1), (R_f = 0.75) as a colourless oil (0.48 mmol, 120 mg, 96% yield). ^1H NMR (300 MHz, $CDCl_3$,): δ = 0.95 [t, J(H,H) = 7.4 Hz, 3 H], 1.39 [sext, J(H,H) = 7.4 Hz, 2 H], 1.63 [quin, J(H,H) = 7.1 Hz, 2 H], 2.22 (*s*, 3 H), 2.54 [t, J(H,H) = 7.2 Hz, 2 H], 2.77 [t, J(H,H) = 7.2 Hz, 2 H], 3.53 (*s*, 2 H), 4.10 [t, J(H,H) = 6.7 Hz, 2 H], 7.20–7.40 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 19.2 (CH_2), 30.7 (CH_2), 33.0 (CH_2), 41.8 (CH_3), 52.9 (CH_2), 62.1

(CH_2), 64.3 (CH_2), 127.0 (CH), 128.2 (2 CH), 129.0 (2 CH), 138.9 (C), 172.7 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2954, 2841, 2791, 1734, 1124 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{15}H_{24}NO_2$: 250.1802 $[M + H]^+$, found 250.1798.

Dibutyl 3,3′-(Isopropylazanediyl)dipropanoate (12l): Isolated after flash chromatography with petroleum ether/NEt_3 (9:1) as a colourless oil (0.351 mmol, 111 mg, 70% yield). ^1H NMR (300 MHz, $CDCl_3$,): δ = 0.85–1.00 (m, 12 H), 1.34 [sext, *J*(H,H) = 7.5 Hz, 4 H], 1.57 [quin, *J*(H,H) = 6.9 Hz, 4 H], 2.38 [t, *J*(H,H) = 7.2 Hz, 4 H], 2.68 [t, *J*(H,H) = 7.2 Hz, 4 H], 2.85 [sept, *J*(H,H) = 6.6 Hz, 1 H], 4.03 [t, *J*(H,H) = 6.6 Hz, 4 H] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (2 CH_3), 18.4 (2 CH_3), 19.2 (2 CH_2), 30.8 (2 CH_2), 34.8 (2 CH_2), 45.8 (2 CH_2), 50.7 (CH), 64.2 (2 CH_2), 173.0 (2 C) ppm. IR (KBr): $\tilde{\nu}$ = 2979, 1733, 1137 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{17}H_{34}NO_4$: 316.24824 $[M + H]^+$, found 316.24873.

Dibutyl 3,3′-(Benzylazanediyl)dipropanoate (12m): Isolated after flash chromatography with petroleum ether/ethyl acetate/NEt_3 (8:2:1), R_f = 0.7, as a colourless oil (0.411 mmol, 150 mg, 82% yield). ^1H NMR (300 MHz, $CDCl_3$,): δ = 0.85 [t, *J*(H,H) = 7.3 Hz, 6 H], 1.28 [sext, *J*(H,H) = 7.3 Hz, 4 H], 1.49 [quin, *J*(H,H) = 6.9 Hz, 4 H], 2.38 [t, *J*(H,H) = 7.2 Hz, 4 H], 2.73 [t, *J*(H,H) = 7.2 Hz, 4 H], 3.52 (*s*, 2 H), 3.98 [t, *J*(H,H) = 6.7 Hz, 4 H], 7.15–7.25 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (2 CH_3), 19.1 (2 CH_2), 30.6 (2 CH_2), 32.7 (2 CH_2), 49.2 (2 CH_2), 58.2 (CH_2), 64.3 (2 CH_2), 127.0 (CH), 128.2 (2 CH), 128.7 (2 CH), 139.1 (C), 172.7 (2 C) ppm. IR (KBr): $\tilde{\nu}$ = 2959, 2873, 1734, 1176 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{21}H_{34}NO_4$: 364.2482 $[M + H]^+$, found 364.2475.

Dibutyl 3,3′-(Cyclohexylazanediyl)dipropanoate (12n): Isolated after flash chromatography with petroleum ether/NEt_3 (9:1) as a colourless oil (0.300 mmol, 107 mg, 60% yield). ^1H NMR (300 MHz, $CDCl_3$,): δ = 0.88 [t, *J*(H,H) = 7.4 Hz, 6 H], 0.95–1.25 (m, 5 H), 1.32 [sext, *J*(H,H) = 7.5 Hz, 4 H], 1.55 [quin, *J*(H,H) = 6.9 Hz, 5 H], 1.60–1.80 (m, 4 H), 2.36 [t, *J*(H,H) = 7.2 Hz, 5 H], 2.73 [t, *J*(H,H) = 7.2 Hz, 4 H], 4.01 [t, *J*(H,H) = 6.6 Hz, 4 H] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (2 CH_3), 19.6 (2 CH_2), 26.2 (2 CH_2), 26.3 (CH_2), 29.2 (2 CH_2), 30.7 (2 CH_2), 34.9 (2 CH_2), 46.3 (2 CH_2), 60.2 (CH), 64.2 (2 CH_2), 172.9 (2 C) ppm. IR (KBr): $\tilde{\nu}$ = 2934, 2878, 1730, 1181 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{20}H_{38}NO_4$: 356.27954 $[M + H]^+$, found 356.2797.

Dibutyl 3,3′-(Butylazanediyl)dipropanoate (12p): Isolated after flash chromatography with petroleum ether/NEt_3 (9:1) as a colourless oil (0.484 mmol, 160 mg, 97% yield). ^1H NMR (300 MHz, $CDCl_3$,): δ = 0.80–0.95 (m, 9 H), 1.15–1.40 (m, 8 H), 1.55 [quin, *J*(H,H) = 7.5 Hz, 4 H], 2.35 [*q*, *J*(H,H) = 7.5 Hz, 6 H], 2.71 [t, *J*(H,H) = 7.3 Hz, 4 H], 4.01 [t, *J*(H,H) = 6.7 Hz, 4 H] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (2 CH_3), 14.0 (CH_3), 19.1 (2 CH_2), 20.4 (CH_2), 29.3 (CH_2), 30.6 (2 CH_2), 32.6 (2 CH_2), 49.2 (2 CH_2), 53.4 (CH_2), 64.2 (2 CH_2), 172.8 (2 C) ppm. IR (KBr): $\tilde{\nu}$ = 2960, 2934, 2873, 1734, 1189 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{18}H_{36}NO_4$: 330.2639 $[M + H]^+$, found 330.2632.

Dibutyl 3,3′-(2-Benzoylhydrazine-1,1-diyl)dipropanoate (12r): Isolated after flash chromatography with petroleum ether/ethyl acetate (3:7) as a white solid (from 0.508 mmol amine substrate used, 0.447 mmol, 176 mg, 88% yield). M.p. 77–79 °C. ^1H NMR (300 MHz, $CDCl_3$,): δ = 0.85 [t, *J*(H,H) = 7.2 Hz, 6 H], 1.26 [sext, *J*(H,H) = 7.3 Hz, 4 H], 1.48 [quin, *J*(H,H) = 7.1 Hz, 4 H], 2.57 [t, *J*(H,H) = 6.7 Hz, 4 H], 3.25 [t, *J*(H,H) = 6.6 Hz, 4 H], 3.94 [t, *J*(H,H) = 6.5 Hz, 4 H], 7.18 (*s*, 1 H) 7.35–7.45 (m, 2 H), 7.45–7.55 (m, 1 H), 7.72 [*d*, *J*(H,H) = 7.6 Hz, 2 H] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (2 CH_3), 19.0 (2 CH_2), 30.5 (2 CH_2), 32.7 (2 CH_2), 52.6 (2 CH_2), 64.6 (2 CH_2), 127.0 (2 CH), 128.6 (2 CH), 131.8 (CH), 133.0 (C), 166.6 (C), 172.8 (2 C) ppm. IR (KBr): $\tilde{\nu}$ = 3226, 2958, 2871, 1730, 1649, 1180 cm^{-1}. $C_{21}H_{32}N_2O_5$ (392.49): calcd. C 64.26, H 8.22, N 7.14; found C 64.24, H 8.10, N 6.72. HRMS (ESI) *m/z* calcd. for $C_{21}H_{33}N_2O_5$: 393.2384 $[M]^+$, found 393.2376.

Supporting Information (see footnote on the first page of this article): Additional data, all experimental procedures and characterizations, copies of ^1H and ^{13}C NMR spectra of all final products, copies of HR mass spectra of new compounds.

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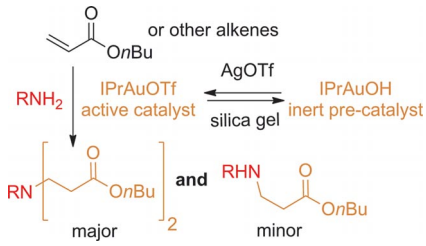
Gold-catalyzed hydroamination reactions of activated alkenes with nitrogen substrates were investigated. Among the various products obtained from these aza-Michael reactions, rare and original dihydroamination products were synthesized with good selectivities. Gold NHC catalyst could be recovered as the hydroxy complex and reused for catalysis when combined with silver triflate.



Keywords: Homogeneous catalysis / Gold / Hydroamination / Aza-Michael reaction / Alkenes / Amines

