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SHORT COMMUNICATION

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Gold-Catalyzed Mannich Addition Reactions of 1,3-Dicarbonyl Compounds with *N*-Protected Imines

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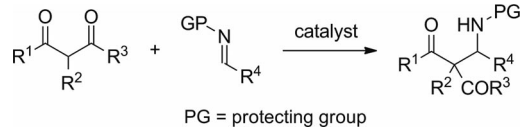
The first (N-heterocyclic carbene)Au^{I}-catalyzed Mannich addition reactions of *N*-protected imines with different 1,3-dicarbonyl compounds are described. $IPrAuNTf_2$ was proven to be an efficient catalyst for the reactions of β-keto esters and 1,3-diketones with *N*-sulfonylimines to afford the desired β-amino carbonyl compounds in good yields under very mild conditions.

Introduction

In the last decade, gold complexes have emerged as efficient catalysts for C–C bond-forming reactions.[1] In this context, nucleophilic additions to the C–C multiple bonds of alkynes, allenes, and alkenes, as well as to the C=O bond of carbonyl groups, are definitely the most common reactivity pattern in gold-catalyzed organic reactions.[1,2] In contrast, only a few examples of gold-catalyzed nucleophilic additions to C=N bonds have been published.[3] Additionally, although gold catalysts have been shown to promote the addition of 1,3-dicarbonyl compounds to C–C multiple bonds,[1a] the addition to imine C=N bonds (Scheme 1) remains, to the best of our knowledge, unknown with this metal. The intermolecular Mannich reaction is the traditional method used to prepare β-amino carbonyl compounds that usually serve as versatile intermediates and important building blocks in the synthesis of products with biological activities.[4] Given the importance of Mannich bases, a wide variety of organocatalysts[5] and metal complexes[6] have been studied as catalysts in direct Mannich addition reactions of 1,3-dicarbonyl compounds to imines.



Scheme 1. Mannich addition of 1,3-dicarbonyl compounds to imines.

Taking into account the catalytic capabilities of gold(III) chloride in three-component Mannich reactions of aldehydes, alkynes, and carbamates,[7] we wondered if we could use gold(I) N-heterocyclic carbene (NHC) complexes as catalysts in the Mannich addition of 1,3-dicarbonyl compounds to imines. Such (NHC)Au units have been described in a number of cases to promote interesting catalytic transformations.[8]

Results and Discussion

Initially, the reaction of β-keto ester **1a** with *N*-tosyl-α-imino ester **2a** in CH_2Cl_2 was chosen as the model reaction (Table 1). If 5 mol-% of the neutral complex IPrAuCl[9] [IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene] was employed as the catalyst precursor, no reaction was observed at room temperature after 24 h (Table 1, entry 1). In view of this result, we decided to check the catalytic activity of different cationic gold complexes, either well defined or in situ generated. Thus, the use of an equimolar mixture of IPrAuCl and $NaBAr'_4$ as a halide scavenger [Ar′ = 3,5-bis(trifluoromethyl)phenyl] induced the targeted reaction and provided **3aa** in 50% yield with 58:42 *dr* (24 h, r.t.; Table 1, entry 2). Additionally, the reaction carried out with $[IPrAu(NCMe)]BF_4$[8d] afforded the two diastereoisomers (56:44 *dr*) in 52% yield after 12 h (Table 1, entry 3).

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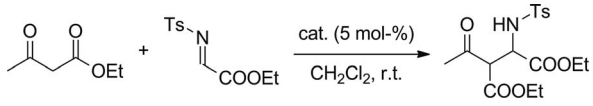
Table 1. Mannich addition of β-keto ester **1a** to *N*-tosyl-α-imino ester **2a** with $IPrAu^{I}$ complexes.[a]

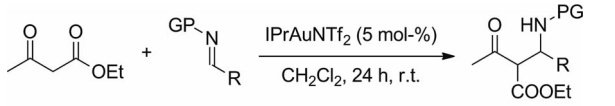


1a **2a** **3aa**

Entry	Catalyst	*t* [h]	Yield[b] [%]	*dr*[c]
1	IPrAuCl	48	0	–
2	IPrAuCl + $NaBAr'_4$	24	50	58:42
3	$IPrAu(NCMe)^+BF_4^-$	12	52	56:44
4	$IPrAuNTf_2$	12	95	56:44
5	$AuCl(SCH_3)_2$	12	40	66:34
6	$IPrAuBr_3$ + $AgNTf_2$	12	51	56:44

[a] Reaction conditions: gold complex (0.0125 mmol), imine (0.3 mmol), β-keto ester (0.25 mmol), CH_2Cl_2 (2 mL). [b] Isolated yield. [c] Diastereomeric ratio (major/minor); determined by analysis of the crude reaction mixture by ^1H NMR spectroscopy.

Table 2. Mannich addition of β-keto ester **1** with imines **2b**–**f** catalyzed by $IPrAuNTf_2$.



1a **2b–f** **3ab–af**

Entry	Imine	PG	R	Product, yield[a] [%]	*dr*[b]
1	**2b**	Ts	*p*-$NO_2C_6H_4$	**3ab**, 84	58:42
2	**2c**	Ts	C_6H_5	**3ac**, 45	58:42
3	**2d**	Ts	*p*-$MeOC_6H_4$	**3ad**, 31	51:49
4	**2e**	Boc	C_6H_5	**3ae**, trace	–
5	**2f**	PMP	CO_2Et	**3af**, trace	–

[a] Isolated yield. [b] Diastereomeric ratio (major/minor); determined by analysis of the crude reaction mixture by ^1H NMR spectroscopy. PG = *N*-Boc (*tert*-butoxicarbonyl); *N*-PMP (*p*-methoxyphenyl).

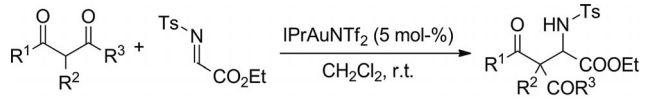
Fortunately, complex $IPrAuNTf_2$,[10] with a weakly coordinating counteranion, showed higher catalytic activity, and it gave the Mannich adduct as a 56:44 diastereomeric mixture in 95% yield at room temperature in 12 h (Table 1, entry 4). The need for a NHC as ancillary ligand was demonstrated by carrying out the reaction with $AuCl(SCH_3)_2$ (5 mol-%; Table 1, entry 5), which afforded the product in only 40% yield. Because free NHCs have been recently described as organocatalysts in Michael additions of 1,3-dicarbonyl compounds,[11] we carried out NMR spectroscopic experiments to check if dissociation of the IPr ligand from the metal center had occurred. In this regard, a solution of $IPrAuNTf_2$ was treated with $B(C_6F_5)_3$, which is known to react with IPr carbene.[12] We monitored the reaction for several hours and found no spectroscopic evidence for the IPr-$B(C_6F_5)_3$ adduct that could eventually form upon dissociation of the IPr ligand from the gold center. Additionally, when we generated the IPr carbene in situ by treatment of $IPrH^+Cl^-$ with NaO*t*Bu in CH_2Cl_2 or in THF, the Mannich adduct was obtained in 25 or 28% yield, respectively. Finally, the gold(III) $IPrAuBr_3$ complex was also tested as a catalyst precursor in the presence of $AgNTf_2$ (1 equiv.). Although active, only 51% yield was obtained under the same reaction conditions (Table 1, entry 6).

Encouraged by these results, we decided to extend the study to other imines derived from simple aldehydes and with different protecting groups (PGs). Therefore, we examined the reaction of **1a** with *N*-*p*-toluenesulfonyl-protected imines **2b**–**d** (Table 2, entries 1–3). As expected, the highest yield was obtained with imine **2b** bearing the NO_2 electron-withdrawing group (Table 2, entry 1), whereas the yield decreased when moving to more electron-donating groups (H and MeO; Table 2, entries 2 and 3). We observed that the protecting group on the imine also affected the reaction: the *N*-tosyl imines gave the products in the highest yields, but the *N*-Boc (*tert*-butoxycarbonyl) and *N*-PMP (*p*-methoxyphenyl) imines gave the products in significantly lower yields (Table 2, entries 4 and 5).

Once the catalytic capabilities of the $IPAuNTf_2$ complex had been demonstrated for this transformation, we extended the scope to other nucleophiles (Table 3). More sterically hindered β-keto esters with substituents at the α-position were essayed with *N*-tosyl-α-imino ester **2a** in the presence of $IPrAuNTf_2$ (5 mol-%). The β-keto ester **1b** possessing a methyl substituent reacted with **2a** to give γ-keto α-amino acid ester **3ba** in 74% yield with 64:36 *dr* after 12 h (Table 3, entry 1). As for **1b**, five- and six-membered cyclic β-keto esters **1c** and **1d** underwent the Mannich reaction to afford **3ca** and **3da**, respectively, in moderate yields and diastereoselectivities (Table 3, entries 2 and 3). In contrast, longer reaction times were necessary to achieve good yields with β-keto ester **1e** possessing an *n*-propyl substituent in the R^1 position (Table 3, entries 4 and 5). The size of the ester moiety in the β-keto esters was also shown to have a significant influence on reactivity and diastereoselectivity. Thus, the reaction of isopropyl derivative **1f** afforded the product in 70% yield after 24 h with low diastereoselectivity (61:39 *dr*; Table 3, entry 6), whereas *tert*-butyl analogue **1g** afforded the product in a decreased yield of 53%, although an increase in the diastereoselectivity was observed (81:19 *dr*; Table 3, entry 7).

1,3-Diketones have been employed to a lesser extent in Mannich reactions. We are aware of just one example of its use with phosphoric acid derivatives as organocatalysts.[5d] We wondered if our system could be extended to acyclic and cyclic 1,3-diketones. Using the same reaction conditions (5 mol-% of $IPrAuNTf_2$, CH_2Cl_2, r.t.), an array of 1,3-diketones were examined (Table 3, entries 8–12). In general, the reactivity did not vary significantly relative to that observed for β-keto esters. 1,3-Diketone **1i**, with a methyl group in the α-position, afforded Mannich adduct **3ia** in 74% yield (Table 3, entry 9). Moreover, five- and six-membered cyclic diketones **1j** and **1k** gave rise to the corresponding Mannich adducts with moderate diastereoselectivity in 89 and 72% yield, respectively (Table 3, entries 10 and 11). Diketone **1l** with a bulkier *tert*-butyl group in the R^3 position proved to be less reactive (Table 3, entry 12).

Table 3. Mannich addition of 1,3-dicarbonyl compounds **1b**–**l** with *N*-tosyl-α-imino ester **2a** catalyzed by $IPrAuNTf_2$.

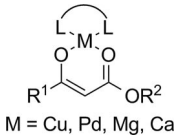


1b–l **2a** **3ba–la**

Entry	**1**	R^1	R^2	R^3	*t* [h]	Product, yield[a] [%]	*dr*[b]
1	**1b**	Me	Me	OEt	12	**3ba**, 74	64:36
2	**1c**	$(CH_2)_3$		OEt	24	**3ca**, 70	80:20
3	**1d**	$(CH_2)_4$		OEt	12	**3da**, 62	72:28
4	**1e**	*n*Pr	H	OEt	12	**3ea**, 55	74:26
5	**1e**	*n*Pr	H	OEt	24	**3ea**, 70	70:30
6	**1f**	Me	H	O*i*Pr	24	**3fa**, 70	61:39
7	**1g**	Me	H	O*t*Bu	24	**3ga**, 53	81:19
8	**1h**	Me	H	Me	12	**3ha**, 63	–
9	**1i**	Me	Me	Me	12	**3ia**, 74	–
10	**1j**	$(CH_2)_3$		Me	12	**3ja**, 89	76:24
11	**1k**	$(CH_2)_4$		Me	12	**3ka**, 72	84:16
12	**1l**	Me	H	*t*Bu	24	**3la**, 65	65:35

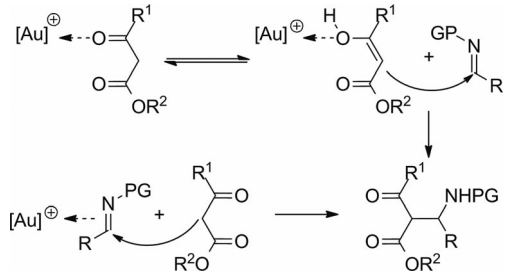
[a] Isolated yield. [b] Diastereomeric ratio (major/minor); determined by analysis of the crude reaction mixture by ^1H NMR spectroscopy.

From a mechanistic point of view, previous catalytic systems based on copper, palladium, magnesium, and calcium have been proposed to proceed with the intermediacy of a species with the dicarbonyl substrate bonded to the metal in a κ^2 fashion (Scheme 2).[6a,6c,6g,6i,6k] Sodeoka and coworkers performed[6c] interesting NMR studies demonstrating that the keto enolate form prevails over the ester enolate, and they also observed a significant shift in the ^{13}C NMR resonances of the carbonyl groups of the bonded and nonbonded substrate. In our case, the well-known tendency of gold(I) to form linear, two-coordinated complexes seems to disfavor the chelating coordination of the dicarbonyl reactant. In fact, monitoring of a 1:1 mixture of the catalyst precursor $IPrAuNTf_2$ with **1a** and **2a** (as in Table 1) by $^{13}C\{^1H\}$ NMR spectroscopy showed no resonances that could be attributable to carbonyl and/or imine coordination. Therefore, the activation of one or more substrates by the metal center must occur at a rate that escapes the NMR timescale.



Scheme 2. Metal enolate intermediate proposed in Mannich reactions.

Given that Lewis acid catalysts have been described to activate the reactants in Mannich-type reactions[13] through the formation of an acid–base adduct, we believe this could be a reasonable explanation in this gold-based system. As shown in Scheme 3, coordination of the dicarbonyl[14] or the imine could be invoked to trigger the catalytic reaction. In the former case, the propensity for linear coordination would support a κ^1 adduct, whereas in the latter case, the side-on coordination of the imine could be favored on the basis of exclusive σ donation of the IPr ligand, which would, therefore, allow π backdonation of the gold center to the molecular orbital of the double bond of the imine. Either way, the corresponding activated reactant would attack a free, noncoordinated molecule of the other to induce the formation of the Mannich adduct. We are currently exploring this transformation to ascertain the role of the gold center in the overall reaction.



Scheme 3. Possible gold(I) activation mechanisms in the Mannich reactions.

Conclusions

In conclusion, we have found that the $IPrAuNTf_2$ complex efficiently catalyzes the Mannich addition reaction of 1,3-dicarbonyl compounds to *N*-protected imines. The examples provided herein are the first examples involving the use of this metal for this transformation. Good yields were obtained for an array of substrates under very mild reaction conditions.

Experimental Section

General Catalytic Procedure for the Mannich Reactions: β-Keto ester or diketone **1a**–**l** (0.25 mmol), imine **2a**–**f** (0.3 mmol), $IPrAuNTf_2$ (5 mol-%), and CH_2Cl_2 (2 mL) were added to a Schlenk tube equipped with a magnetic stirring bar. The reaction mixture was stirred at room temperature for 12–24 h under a N_2 atmosphere. The volatiles were removed under vacuum, and the residue was purified by column chromatography on silica gel.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and ^1H NMR and ^{13}C NMR spectra of the products.

Acknowledgments

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