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Gold(I) or Silver Catalyzed Synthesis of α-Indolylacrylates

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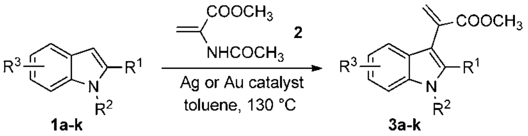
ABSTRACT



11 examples
21-93% yield

Methyl 2-acetamidoacrylate reacted with various 2-substituted indoles in the presence of catalytic amounts of AgSbF$_6$ or AuPPh$_3$NTf$_2$ to provide the corresponding methyl 2-(2-substituted-1*H*-indol-3-yl)acrylates.

The synthesis of indole derivatives through the direct functionalization of the indole nucleus is a widespread research area and had been and remains an exciting topic in organic synthesis. The C3 functionalization of the indole nucleus through the formation of a new carbon–carbon bond has been traditionally achieved by Friedel–Crafts alkylation and acylation reactions featuring the well-recognized reactivity of this electron-rich heteroaromatic system.[1] More recently, the introduction of innovative catalytic and organocatalytic processes widened the scope of these reactions and, consequently, the chance to achieve complex and intriguing architectures with high regioselectivity, avoiding dimerization and polymerization reactions, and in selected cases in a stereocontrolled fashion.[2] *Inter alias*,[3] Piersanti[4] reported an efficient C3 alkylation of indoles with α-amidoacrylate where the regioselectivity (conjugate (*β*) vs α alkylation) was achieved by switching from oxo- to aza-philic Lewis acids (Scheme 1). On the other hand, Arcadi[5] reported the C3 regioselective alkylation of indoles through gold-catalyzed conjugated addition type reactions with α,*β*-enones (Scheme 1).

In this work we want to report our findings about the reaction of indole derivatives with methyl 2-acetamidoacrylate in the presence of catalytic amounts of cationic gold(I) complexes and silver or gold(III) salts (Scheme 1).

We started our investigations taking into account the results obtained by Arcadi on the C3 regioselective alkylation of indoles through gold-catalyzed conjugated addition-type reactions with α,*β*-enones. These reactions, performed in ethanol at room temperature and in the

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[1] (a) Sundberg, R. J. *Indoles*; Academic Press: London, U.K., 1996. (b) Brown, R. K. *Indoles*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, US, 1972. (c) Trofimov, B. A.; Nedolya, N. A. In *Comprehensive Heterocyclic Chemistry*; Jones, G., Ramsden, C. A., Eds.; Elsevier: Oxford, U.K., 2008; Vol. 3, pp 88–168.

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Scheme 1. Routes to C3 Functionalized Indoles

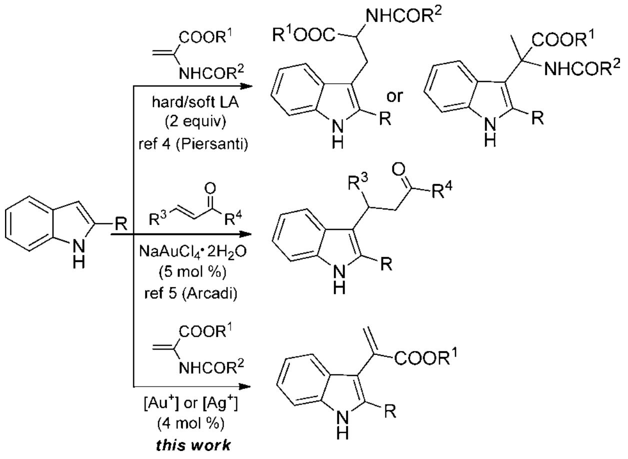
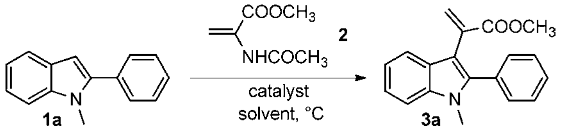


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	solvent	temp (°C)	time (h)	3a[b] (%)
1	$NaAuCl_4 \cdot 2H_2O$ (5)	EtOH	70	24	30
2	–	toluene	130 (mw)	6[a]	–
3	$NaAuCl_4 \cdot 2H_2O$ (4)	DCM	60	30	–
4	$AuCl_3$ (4)	toluene	130	48	–
5	$AuPPh_3Cl/AgOTf$ (2)	EtOH	70	30	–
6	$AuPPh_3Cl/AgOTf$ (2)	EtOH	100 (mw)	6	–
7	$AuPPh_3Cl/AgOTf$ (2)	DMF	100 (mw)	6	–
8	$AuPPh_3Cl/AgOTf$ (2)	DCE	130 (mw)	6	31
9	$AuPPh_3Cl/AgOTf$ (2)	MeCN	100 (mw)	6	48
10	$AuPPh_3Cl/AgOTf$ (2)	$CHCl_3$	100 (mw)	6	60
11	$AuPPh_3Cl/AgOTf$ (2)	toluene	130	6	74
12	$AuPPh_3Cl/AgOTf$ (2)	toluene	130 (mw)	6	70
13	**$AuPPh_3Cl/AgOTf$ (4)**	**toluene**	**130**	**6**	**80**
14	Au(IPr)Cl/AgOTf (4)	toluene	130	6	76
15	$AuPPh_3OTf$ (4)[7]	toluene	130	6	75
16	**$AuPPh_3NTf_2$ (4)**	**toluene**	**130**	**6**	**79**
17	AgOTf (4)	toluene	130	6	74
18	**$AgSbF_6$ (4)**	**toluene**	**130**	**3**	**83**
19	$AgNTf_2$ (4)	toluene	130	3	85

[a] Reaction conditions: dry solvent (5 mL), **1a** (0.5 mmol), and **2** (0.55 mmol). [b] Isolated yield.

presence of 5 mol % $NaAuCl_4 \cdot 2H_2O$, afforded the corresponding alkylated indoles in good yields. However, when we reacted the 1-methyl-2-phenylindole **1a** with α-amidoacrylate **2** under the same reaction conditions no reaction occurred at rt, whereas, surprisingly, at 70 °C methyl 2-(1-methyl-2-phenyl-1*H*-indol-3-yl)acrylate **3a** was isolated in 30% yield (Table 1, entry 1). The novelty of the achieved transformation and the remarkable structure of the obtained compound prompted us to investigate both the catalyst/solvent system and the reaction mechanism. Indeed, 2-(1*H*-indol-3-yl)acrylates are scarcely described in the literature and were prepared mainly by addition/elimination sequences.[6] Therefore, using **1a** and **2** in a model reaction, a comprehensive review of reaction conditions we tested for the synthesis of **3a** is summarized in Table 1.

The reaction failed in the absence of catalysts, in the presence of sodium tetrachloroaurate in dichloromethane or of gold(III) chloride in toluene (entries 2–4). The cationic gold(I) complex $AuPPh_3OTf$, generated in situ from triphenylphosphine gold(I) chloride and silver triflate, gave scarce results in ethanol under conventional heating (70 °C), under microwave irradiation (100 °C) and in dimethylformamide (entries 5–7). Moderate yields of the desired compound **3a** were obtained with the same catalyst in 1,2-dichloroethane, acetonitrile, and chloroform (entries 8–10), whereas better results were achieved in toluene under conventional heating (screw cap tube, 130 °C), under microwave irradiation (130 °C), or by doubling the catalyst loading, giving rise to compound **3a** in 74%, 70%, and 80% yield, respectively (entries 11–13). The presence of cationic *N*-heterocyclic carbene gold(I) species slightly affected the reaction course (entry 14). Silver free catalysts, triphenylphosphinegold(I) triflate[7] and gold(I) bis(trifluoromethanesulfonyl)imide, afforded **3a** in comparable yields (entries 15–16). On the other hand, also silver salts (silver triflate, silver hexafluoroantimonate, and silver bis(trifluoromethanesulfonyl)imide) very efficiently catalyzed the reaction, although slightly better yields of **3a** and shorter reaction times were observed using $AgSbF_6$ and $AgNTf_2$ (entries 17–19). Finally, in all reported examples, the counterion structure appeared to exert a minor effect on the reaction course. Therefore, the conditions reported in entries 13 and 16, for the cationic gold(I)-catalyzed reactions, and in entry 18, for the silver-catalyzed reactions, were chosen as standard conditions to survey the generality of the reaction with various substituted indoles (Table 2). Dielectric heating was discharged because it was unnecessary for the purpose, and cheap $AgSbF_6$ was preferred over the more expensive $AgNTf_2$. Entry 1 reports the results obtained in the model reaction with the best performing catalysts. The reaction worked well also with *N*-unsubstituted indole **1b** even if in this case cationic gold(I) catalysts seemed to be superior to the silver salt, entry 2. Since $AuPPh_3NTf_2$ gave better results than $AuPPh_3Cl/AgOTf$, it was employed in the succeeding experiments. Good results were obtained with 2-phenylindoles bearing both electron-withdrawing or -donating substituents in position 5 or 6 at the indole nucleus (entries 3–6) or on the aryl moiety (entries 7–8). A 3-thiophenyl substituent at C2 was tolerated as well as a methyl substituent (entries 9–11). In general, *N*-methyl indoles gave comparable results to *N*-unsusbstituted

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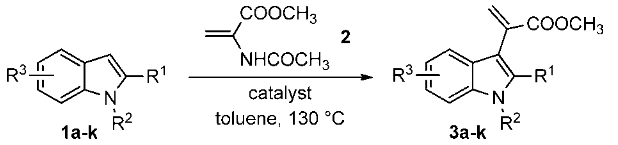
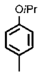
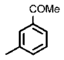
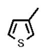
indoles (i.e., *cfr.* entries 1, 3, and 10 with entries 2, 4, and 11, respectively). Nevertheless, the reaction outcome was proven to be completely altered when 2-unsubstituted-*N*-methylindole **1l** was chosen as substrate (Scheme 2). Thus, under gold catalysis at 130 °C, methyl 2,2-bis(1-methyl-1*H*-indol-3-yl)propanoate **4** was isolated as the main reaction product besides unreacted **1l** and a mixture of unidentified tarry compounds, whereas at 80 °C **4** was obtained in 59% yield besides unreacted **1l**. Similar results were also obtained using a silver catalyst.

Table 2. Scope of the Reaction[a]

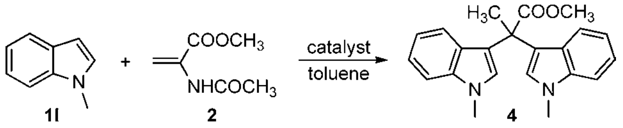


	1	R^1	R^2	R^3	h	Catalyst	3, %[b]
1	**a**	C_6H_5	CH_3	H	6	$AuPPh_3Cl/AgOTf$	80
					3	$AgSbF_6$	83
					6	$AuPPh_3NTf_2$	79
2	**b**	C_6H_5	H	H	6	$AuPPh_3Cl/AgOTf$	76
					6	$AgSbF_6$	60
					6	$AuPPh_3NTf_2$	93
3	**c**	C_6H_5	CH_3	5-OMe	23	$AgSbF_6$	76
					23	$AuPPh_3NTf_2$	71
4	**d**	C_6H_5	H	5-OMe	23	$AgSbF_6$	62
					23	$AuPPh_3NTf_2$	70
5	**e**	C_6H_5	H	6-CF_3	6	$AgSbF_6$	46
					6	$AuPPh_3NTf_2$	50
6	**f**	C_6H_5	H	5-NHAc	6	$AgSbF_6$	53
					6	$AuPPh_3NTf_2$	68
7	**g**	 OiPr	H	H	6	$AgSbF_6$	76
					24	$AuPPh_3NTf_2$	21
8	**h**	 COMe	H	H	6	$AgSbF_6$	76
					6	$AuPPh_3NTf_2$	78
9	**i**	 S	H	H	6	$AgSbF_6$	51
					5	$AuPPh_3NTf_2$	82
10	**j**	CH_3	CH_3	H	4	$AgSbF_6$	63
					4	$AuPPh_3NTf_2$	73
11	**k**	CH_3	H	H	6	$AgSbF_6$	62
					6	$AuPPh_3NTf_2$	87

[a] Reaction conditions: dry toluene (5 mL), catalyst (4 mol %), **1** (0.5 mmol), and **2** (0.55 mmol). [b] Isolated yield.

The reported reactions are regiospecific, and the new carbon–carbon bond is formed solely between the C3 of the indole nucleus and the α-carbon of the dehydroamino acid. Moreover, considering a plausible reaction mechanism we could reasonably disregard a mechanism involving a heterocyclic C_{sp^2}–H activation step. Indeed, under gold(I) catalysis, C_{sp^2}–H bond activation has been demonstrated to be consistent only for non-electron-rich substrates.[8] Moreover, 3-benzofuranyl and 3-indolylgold(I) derivatives have been isolated and characterized by Hashmi as a quite stable intermediate in gold(I)-catalyzed hydrooxylation and hydroamination reactions of *ortho*-alkynylphenols and anilines,[9] but they easily undergo a deauration reaction and cannot be directly prepared from the corresponding benzofuran or indole derivatives and gold(I). Besides, in the presence of hard or soft Lewis acids, σ-activation by interaction, respectively, with amide carbonyl oxygen or amide nitrogen of **2** has been invoked, evidenced by ^1H NMR experiments, to explain the α versus β selectivity observed in the addition of indoles to dehydroalanine.[4,10] Analogous ^1H NMR experiments performed in benzene-d_6 with **2** in the presence of an equimolecular amount of cationic gold(I) or Ag species did not show any significant chemical shift variation or broadening in the signals with respect to pure **2** thus discounting the formation of an electrophilic *N*-acylimine intermediate (Scheme 3).

Scheme 2. Behaviour of 2-Unsubstituted Indoles



1l:**2** = 1:1.1, $AuPPh_3Cl$ (2)/AgOTf (2), 130 °C, 6 h, 26%
1l:**2** = 2:1, $AuPPh_3Cl$ (2)/AgOTf (2), 80 °C, 48 h, 59%
1l:**2** = 2:1, AgOTf (2), 80 °C, 48 h, 56%

Most probably, we could regard the reactions involving 2-substituted indoles **1a**–**k** as involving the simultaneous addition of an electrophile (the metal) and a nucleophile (the indole) to the C=C double bond of **2** to give intermediate **I**, followed by fast thermal and proton assisted elimination of acetamide (intermediate **II**), rearomatization of the heterocyclic nucleus, and regeneration of the catalyst (Scheme 3). The intermediacy of conjugated structures like **II** has been reported for the reaction of indoles with carbonyl compounds.[11] However, considering that the reaction medium is somewhat acidic, protonation of the acetamido moiety prior to elimination cannot be excluded. In order to shed light on this point we performed several control experiments by reacting **1a** with **2** in the

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(7) The catalyst was prepared by mixing an equimolecular amount of $AuPPh_3Cl$ and AgOTf in dry toluene. The obtained suspension was filtered through a syringe fitted with a Whatman Anotop 10 IC filter to remove the AgCl precipitate. The solution was then charged with the reactants as reported in Table 1.

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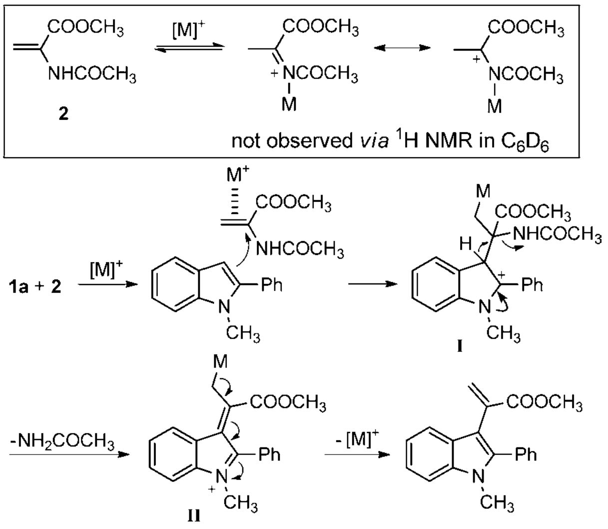
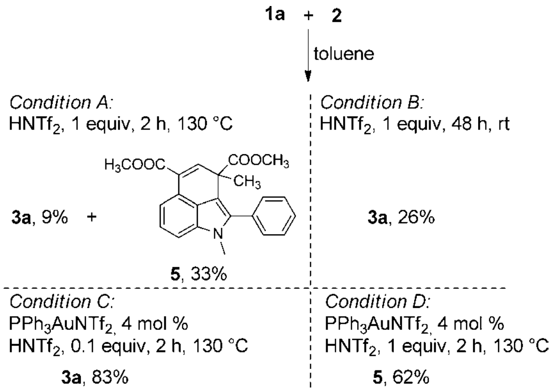
Scheme 3. Proposed Reaction Mechanism for Compounds **3a**−**k**



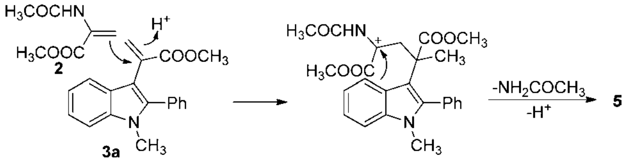
presence of 1 equiv of $HNTf_2$ in toluene at 130 °C and at rt (Scheme 4, conditions A and B), and under the standard conditions reported in Table 1 entry 16 in the presence of 0.1 and 1 equiv of $HNTf_2$ (Scheme 5, conditions C and D). Triflimide was chosen as an acidic promoter in order to avoid modification in the counterion structure.

Scheme 4. Reaction of **1a** and **2** under Modified Conditions



The use of $HNTf_2$ as a cocatalyst, at a concentration of 0.1 equiv, did not alter the reaction outcome (C), suggesting the elimination of the acetamido moiety from intermediate **I** did not benefit from the presence of excess acid and the reaction outcome is most probably related to the intrinsic electrophilic properties of Au^+ and Ag^+ species able to promote the addition of the nucleophile to **2** in the first step of the reaction and to be easily released from intermediate **II** under thermal conditions. Moreover, sole $HNTf_2$ in a stoichiometric amount was a poor promoter for the reaction of **1a** with **2** at rt (B), whereas at 130 °C it promoted the formation of compound **5** which has been isolated and characterized along with a mixture of tarry side products (A). Finally, **5** was again the main reaction product running the reaction under standard conditions but in the presence of 1 equiv of $HNTf_2$ (D). Accordingly with the obtained results, we can reasonably rule out a mechanism involving pure protic catalysis for the formation of **3**. Moreover, **5** was formed probably *via* proton catalyzed addition of a second molecule of **2** to **3** followed by electrophilic aromatic substitution on C-4 of the indole nucleus and loss of acetamide (Scheme 5).

Scheme 5. Proposed Reaction Mechanism for Compound **5**



The reaction mechanism reported in Scheme 4 also accounts for the behavior of 2-unsubstituted indole **1l** (Scheme 2). The formation of **4** from **1l** may likely take place through conjugate addition of a second molecule of **1l** to an intermediate like **II**. A similar mechanism has been previously suggested starting from indole itself and **2** under silica-supported Lewis acid catalysis.[12] An analogous behavior is not allowed for 2-substituted indole, as the elimination pathway is probably favored by steric hindrance and by the high reaction temperature involved.

In conclusion, this chemistry highlights new aspects of gold and silver catalysis and, more importantly, this approach is amenable to a convenient access to quite unknown compounds which could represent viable starting materials for the achievement of a more complex structure by, i.e., cycloaddition or addition reactions eventually included in multicomponent or cascade processes.

Supporting Information Available. Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) de la Hoz, A.; Díaz-Ortiz, A.; Gómez, M. V.; Mayoral, J. A.; Moreno, A.; Sánchez-Migallón, A. M.; Vásquez, E. *Tetrahedron* **2001**, *57*, 5421.

The authors declare no competing financial interest.