

Gold(III) chloride promoted addition of electron-rich heteroaromatic compounds to the C=C and C=O bonds of enals

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Abstract—Electron-rich heteroaromatic compounds react with α,β -enals in the presence of gold(III) chloride to afford bis-addition products in high yields.

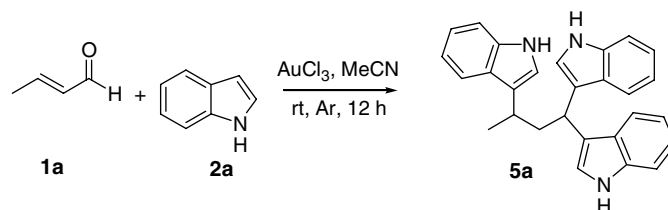
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The direct addition of electron rich heteroaromatic compounds to activated C=C and C=O bonds under mild conditions would constitute an interesting and useful synthetic protocol.¹ It was known as early as in 1931 from the pioneering work of Kharasch and Isbell,² that gold(III) chloride can activate aromatic C–H bonds. The first synthetic application of this process was only recognized in 2000, when Hashmi et al. showed that gold(III) chloride catalyzes the addition of 2-methylfuran with methyl vinyl ketone to give the corresponding hydro-arylated product.^{3,4} Subsequently, a number of other groups, most notably that of Reetz, reported the addition of arenes to triple bonds.⁵ The reports on the addition of arenes to imines and active methylene compounds to alkenes are also noteworthy.⁶ Recently, we reported a very efficient gold(III) chloride promoted reaction of aldehydes and electron-rich arenes leading to the synthesis of triaryl and triheteroaryl methanes.⁷ The results obtained in this reaction prompted us to investigate the addition of electron rich heterocycles to enals.

Although Hashmi and Reetz had reported the addition of arenes to enones⁸ and ynones,⁵ such reaction with enals has not been investigated.⁹ It is also worthy of mention that the zirconium triflate catalyzed addition of indole and pyrrole with α,β -unsaturated carbonyl compounds has been reported to afford bis(indolyl)methanes, albeit in moderate yields.¹⁰ The results of our studies are presented here.

In a pilot experiment, indole (**2a**) was treated with crotonaldehyde (**1a**) in the presence of gold(III) chloride (1 mol %) in acetonitrile. After stirring the mixture at room temperature for 12 h, the reaction mixture was processed to afford the tris-addition product **5a**, in 70% yield (Scheme 1). The product **5a** was characterized from spectroscopic data.¹¹

It was found that other heterocycles such as 2-methylfuran and 1-methylindole also reacted efficiently under the same conditions. The reaction also works well with



Scheme 1.

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Table 1. Addition of electron-rich heteroaromatic compounds to α,β -enals

Entry	R ¹	R ²	Yield (%)
1	<i>p</i> -BrPh 1b		5b (85)
2	<i>o</i> -ClPh 1c		5c (92)
3	C ₃ H ₇ 1d		5d (74)
4	C ₃ H ₇ 1d		5e (74)
5	H 1e		5f (94)
6	2-Thienyl 1f		5g (75)

aromatic and aliphatic α,β -unsaturated aldehydes (Table 1).

In some cases, however, two products were obtained: the hydroarylated product and the bis-addition product with the aldehyde (Table 2).

Although the mechanistic details of the reaction are not known, it is reasonable to assume that the C–H activation¹² of arenes by gold(III) chloride contributes to the major reaction pathway. The observation that the products are obtained in very low yields when the reaction was carried out in the presence of Lewis acids such as ytterbium triflate and indium trichloride lends credence to this assumption. It should also be mentioned that products are formed in low yields in the presence of *p*-toluenesulfonic acid.

In general, under gold(III) chloride catalysis, reaction of electron rich aromatic systems with enals give rise to hydrovinylated products.^{9a} Subsequent reaction of the nucleophile, as shown in this paper occurs at the carbonyl group. Evidently the products **6h–j** arise by the addition of the nucleophile to the carbonyl group in preference to conjugate addition. This mechanistic dichotomy may be due to a subtle difference in the orbital coefficient at the β -carbon. Theoretical calculations are likely to throw light on this point. We plan to address this issue and will report the results in a full paper.

Interestingly, bis(indolyl)methanes are known to have applications in research areas such as materials science,¹³ agrochemicals¹⁴ and pharmaceuticals.¹⁵ They also find application in the construction of important indolyl alkaloids such as hapalindoles.¹⁶

In conclusion, we have shown that α,β -unsaturated aldehydes undergo hydroarylation with electron-rich arenes such as indole, 1-methylindole and 2-methylfuran. The experimental simplicity and the high yield of the products are especially noteworthy. Further work will be undertaken to explore the scope of this reaction.

Table 2.

Entry	R ¹	R ²	Yield (%)	Yield (%)
1	Ph 1g		5h (58)	6h (33)
2	Ph 1g		5i (50)	6i (43)
3	2-Naphthyl 1h		5j (71)	6j (17)

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9. While this manuscript was in preparation, we came across two papers pertinent to the above work: (a) one by He et al. in which arenes have been reported to undergo Michael addition to α,β -enals in the presence of AuCl_3 and, (b) the second by Yao et al. describing the CAN catalyzed addition of indole to α,β -unsaturated carbonyl compounds. (a) Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, 690, 5049–5054; (b) Ko, S.; Lin, C.; Tu, Z.; Wang, Y.-F.; Wang, C.-C.; Yao, C.-F. *Tetrahedron Lett.* **2006**, 1, 487–492.
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11. A typical experimental procedure for the preparation of **5a**: A solution of crotonaldehyde **1a** (100 mg, 1.42 mmol) and indole **2** (533 mg, 4.57 mmol) in acetonitrile (3 ml) was purged with argon for 5 min. To this mixture, a solution of AuCl_3 (1 mol %) in 2 ml of acetonitrile was added, and was then stirred under argon for 12 h. After completion of the reaction as indicated by TLC, the solvent was removed under vacuum and the crude product was purified by silica gel column chromatography to afford the product **5a** in 70% yield. Compound **5a**: colourless liquid; IR (neat) ν_{max} : 3413, 1460, 1423, 1260, 1225, 744 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 7.39–6.71 (m, 18H), 4.49 (t, 1H, $J = 7.5$ Hz), 3.07–3.00 (m, 1H), 2.72–2.62 (m, 1H), 2.47–2.37 (m, 1H), 1.39 (d, 3H, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 136.6, 136.5, 127.1, 126.8, 122.5, 121.8, 121.7, 121.4, 120.3, 120.2, 119.8, 119.7, 119.0, 118.9, 111.1, 111.0, 43.7, 31.9, 28.9, 22.0. HRMS (EI) m/z calculated for $\text{C}_{28}\text{H}_{25}\text{N}_3$: 403.2048, found: 403.2038.
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