JOC Notes

Transition Metal Salt-Catalyzed Direct Three-Component Mannich Reactions of Aldehydes, Ketones, and Carbamates: Efficient Synthesis of N-Protected β-Aryl-β-Amino Ketone Compounds

Li-Wen Xu, Chun-Gu Xia,* and Lyi Li

State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, PRC

cgxia@ns.lzb.ac.cn

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Abstract: The transition metal salt-catalyzed direct three-component Mannich reactions of aryl aldehydes, aryl ketones, and carbamates are described. The $RuCl_3{\cdot}xH_2O$-, $AuCl_3{-}PPh_3$-, and $AuCl_3$-catalyzed direct Mannich reactions led to the synthesis of N-protected β-aryl-β-amino ketones, and the results create new possibilities for exploiting the transition metal salt-catalyzed direct Mannich reaction and facile synthesis of β-amino ketone libraries.

Multicomponent coupling reactions (MCRs) are emerging as useful tools for the carbon−carbon and carbon−heteroatom bond-forming reactions and for the synthesis of small druglike molecules with several degrees of structural diversity.[1] Although pioneering work by several research groups in this area has already established the versatility and uniqueness of one-pot multicomponent coupling protocols as a powerful methodology for the synthesis of novel organic nitrogen molecules, a challenging goal in organic chemistry is to link several compounds together in one reaction flask via sequential bond-forming processes.[2,3] The Mannich reaction is one such multicomponent reaction and is the most widely utilized chemical transformation for constructing β-amino ketones and other β-amino carbonyl compounds, which in turn are important synthetic intermediates for various pharmaceuticals, natural products, and so forth.[4] In past decades, the Mannich reaction has gained popularity,[5] and recently, efficient, direct Mannich reactions of aldehydes, ketones, and aryl amines have been realized via transition metal salt catalysis and organocatalytic approaches (L-proline catalysts).[6] However, these strategies for the direct Mannich reaction have a drawback in the limited application of amines or ketones; therefore, the attempt to extend the applicability of catalytic protocols to less-reactive compounds, such as amides, is one of the challenges. To our knowledge, direct Mannich-type carbamates catalyzed by transition metal salts have not been reported. In this paper, we describe, for the first time, the application of several transition metal salt catalysts to direct Mannich-type reactions of aldehydes, ketones, and carbamates to generate N-protected β-aryl-β-amino ketones, which are difficult to synthesize via other procedures.

We are interested in the synthesis of β-amino carbonyl compounds, and direct Mannich-type reactions stem from our results with the analogous aza-Michael reaction. With regard to the importance of transition metal salt catalysts in organic synthesis and the occurrence of β-amino carbonyl compounds in drugs and natural products, we decided to test the catalytic activity of several transition metal salts in the direct three-component Mannich reaction. The synthetic method of the direct use of carbamates could provide the synthesis of β-primary amino ketones because the N-protected groups (carbamates) are easily removed.

In our previous publication,[7] we have shown that aromatic enones reacted with carbamates to afford the β-aryl-β-amino ketones in moderate yield via the aza-Michael reaction. On the basis of these results in the iron-catalyzed aza-Michael reaction of carbamates, we con-

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* Author to whom correspondence should be addressed. Fax: (+86) 931-827-7088. Telephone: (+86) 931-486-8089.

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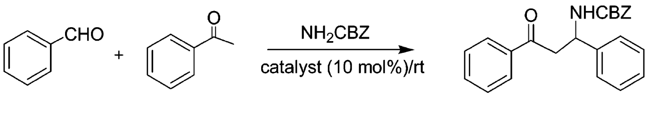
SCHEME 1. Direct Mannich-Type Reactions with Several Transition Metal Salt Catalysts



tinued to study the aza-Michael reaction and the direct classic Mannich reaction of carbamates instead of amines. However, many transition metal salts, such as $AuCl_3$, have no catalytic activities in the aza-Michael reaction of chalcones. Thus, the direct three-component Mannich reaction of benzaldehyde (1 equiv), ethyl carbamate (1.5 equiv), and acetophenone (1 equiv) was selected as a model. Interestingly, it was revealed that the direct Mannich reactions proceed smoothly to afford the desired adducts in moderate yields at room temperature when $FeCl_3$/TMSCl was used as a catalyst system. However, when only $FeCl_3$ was used as a catalyst, it was not effective in this reaction. Several attempts have been made to achieve the direct Mannich reaction with other catalytic transition metal salts. We surveyed various transition metal salts in the three-component Mannich reaction at room temperature (Scheme 1). Interestingly, among the transition metal salts (10 mol %) tested, only $RuCl_3 \cdot xH_2O$, $AuCl_3$, and $AuCl_3-PPh_3$ were found to be effective in the Mannich reaction, and $Cu(OTf)_2$, $Pd(CH_3CN)_2Cl_2$, $RuCl_2(PPh)_3$, $NiCl_2 \cdot 6H_2O$, and $CuCl_2$ were not effective catalysts in the Mannich reactions of benzaldehyde, acetophenone, and benzyl carbamate (NH_2CBZ). No adduct product was obtained in the absence of transition metal salt catalysts when the reaction was carried out at both room temperature and reflux, and L-proline was also found to be a noneffective catalyst in this Mannich reaction.

To increase the efficiency of this process, we selected gold salt as a catalyst and investigated the development of Mannich-type reactions. During the past few years, gold compounds have emerged as powerful Lewis acids and transition metal catalysts for various chemical transformations.[8,9] However, compared to other transition metals, gold has not been extensively explored as a catalyst. Gold-catalyzed homogeneous organic reactions are quite rare, as demonstrated by the recent work of Ito-Hayashi et al., and several reactions have been demonstrated with the unique catalyst properties of gold complexes.[10] Herein, we reveal the catalytic activities of gold complexes in the three-component Mannich-type reactions of aryl aldehydes, aryl ketones, and carbamates.

In the initial exploration of gold as a catalyst, a series of experiments were performed in order to determine the feasibility of using a ketone directly in the gold-catalyzed Mannich-type reactions. We first examined the three-component coupling of benzaldehyde, acetophenone, and benzyl carbamate using a Au catalyst under various reaction conditions. In this reaction, CH_3CN and CH_2Cl_2 were found to be the most effective solvents, and similar results were obtained using $AuCl_3-PPh_3$ or $AuCl_3$ as the catalyst. The reaction catalyzed by $AuCl_3-PPh_3$ was found to proceed smoothly in CH_3CN at room temperature for 24 h to afford a moderate yield of the corresponding β-amino ketone (48% isolated yield), and trace amounts of imine ($\sim$15%) from the reaction of benzaldehyde and carbamate were confirmed; enones ($<$10%) were also detected in this mixture. The formation of imine from carbamate with aldehyde was easily catalyzed by the gold catalyst, and the aldol reactions of benzaldehyde or imine with acetophenone could be carried out with the same gold catalyst. In these different reactions, the formation of imine was a faster step. On the basis of the results obtained here, it is reasonable to propose that three-component condensation reactions proceed in an aldol-type way.[11] It involves (i) the formation of imine by the reaction of aldehyde with carbamate and (ii) the addition of ketone to imine to afford the total β-amino ketone.

On the basis of the above findings, the improved direct three-component Mannich reactions of benzaldehyde (1.0 equiv), acetophenone (5.0 equiv), and ethyl carbamate (1.5 equiv) worked well to give the corresponding β-amino ketones in good yield (83% isolated yield). In addition, the direct three-component Mannich reaction could proceed using 1 mol % $AuCl_3-PPh_3$ with a moderate yield of the corresponding β-amino ketone under mild conditions (59% yield).

Subsequently, with this effective catalyst in hand, we then used the $AuCl_3-PPh_3$ catalyst for the direct Mannich reactions of various electron-rich and electron-poor benzaldehydes and ketones under similar conditions, and in most cases, it was revealed that the three-component reactions proceeded smoothly to afford the desired adducts in good yield, even with less-reactive aldehydes and ketones such as 4-nitrobenzaldehyde and 4-nitroacetophenone. As shown in Table 1, the direct three-component Mannich-type reactions of carbamates smoothly afforded the desired β-amino ketones in good yield. It should be noted that the three-component Mannich reactions are atom-economical and a useful method for the facile synthesis of β-amino ketone libraries.

Next, we reacted the α-tetralone and benzaldehyde with ethyl carbamate to afford the corresponding β-amino ketone **4a**. As shown in Scheme 3, the reaction proceeded smoothly with high diastereoselectivity (with a syn/anti ratio of 85:15) in 80% isolated yield. It was also observed that 4-chlorobenzaldehyde gave a higher and excellent diastereoselectivity with the syn/anti ratio of >99:1 in this Mannich reaction.

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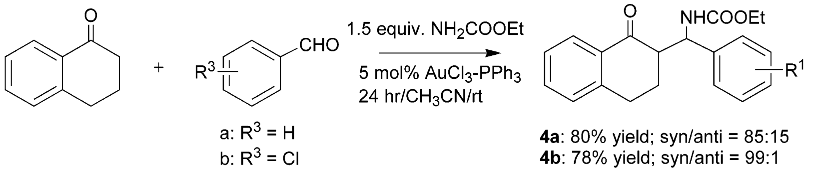
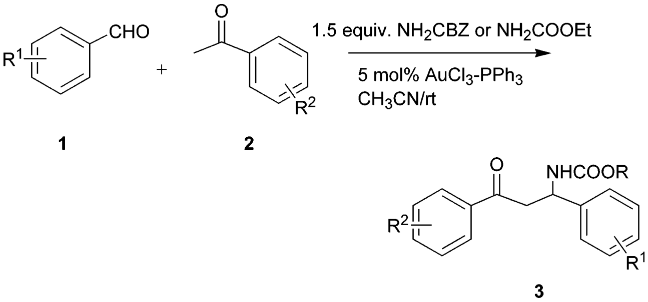
SCHEME 2



4a: 80% yield; syn/anti = 85:15
4b: 78% yield; syn/anti = 99:1

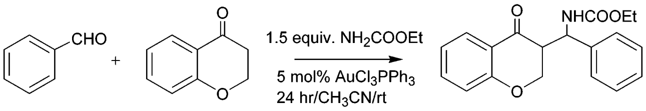
TABLE 1. Gold-Catalyzed Direct Mannich Reactions with Carbamates



entry^a	R^1	R^2	carbamate	time (h)	product (yield,^{b} %)
1	H	H	NH$_2$COOEt	24	**3a** (82)
2	H	*p*-NO$_2$	NH$_2$COOEt	48	**3b** (54)
3	*p*-NO$_2$	H	NH$_2$COOEt	24	**3c** (65)
4	*p*-CH$_3$	H	NH$_2$CBZ	18	**3d** (81)
5	*p*-Cl	H	NH$_2$COOEt	18	**3e** (79)
6	*o*-Cl	H	NH$_2$COOEt	24	**3f** (68)
7	H	*p*-OCH$_3$	NH$_2$COOEt	24	**3g** (60)
8	*p*-Br	H	NH$_2$CBZ	24	**3h** (75)
9	*p*-Cl	*o*-Cl	NH$_2$COOEt	24	**3i** (70)
10	*p*-Cl	*p*-OCH$_3$	NH$_2$CBZ	18	**3k** (62)

[a] Reaction conditions: aldehyde (1 mmol), carbamate (1.5 mmol), ketone (5 mmol), and AuCl$_3$−PPh$_3$ (5 mol %) in CH$_3$CN at room temperature. [b] Isolated yield.

SCHEME 3



5a: syn/anti = 68:32
68% isolated yield

Following this success, we examined another Mannich reaction of 4-chromanone under similar conditions. The desired product **5a** was obtained efficiently in 78% yield with a syn/anti ratio of 68:35. As determined by ^{1}H NMR, the diastereoselectivity remains relatively consistent, favoring the syn product. Although a detailed explanation is unavailable at this moment, asymmetric catalysis based on the catalyst might be possible.

In conclusion, we have developed the first active and general system for the direct three-component Mannich reactions of aryl aldehydes, aryl ketones, and carbamates. From a synthetic point of view, these results create new possibilities for exploiting the transition metal-catalyzed direct Mannich reaction, and the one-pot three-component reaction is an atom-economical synthetic method, as well as a useful method, for the facile synthesis of β-amino ketone libraries.

Experimental Section

Typical Experimental Procedure. To a solution of AuCl$_3$−PPh$_3$ (5 mol %) in CH$_3$CN (1.5 mL) were added ethyl carbamate (1.5 mmol), 4-chlorobenzaldehyde (1.0 mmol), and α-tetralone (5.0 mmol) successively at room temperature. After the mixture was stirred for 24 h, a saturated aqueous NaHCO$_3$ solution (5 mL) and brine (5 mL) were added, and the mixture was extracted with ethyl acetate. The organic phase was dried (Na$_2$SO$_4$) and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified by silica gel chromatography and gave the desired product of **4b**: ^{1}H NMR δ 7.96 (J = 1.2, 8.0 Hz, 1H), 7.48 (J = 7.6 Hz, 1H), 7.23−7.36 (aryl-H, 6H), 5.80 (br s, 1H), 5.08 (dd, J = 5.6, 8.2 Hz, 1H), 4.06 (dd, J = 7.6, 14.2 Hz, 3H), 3.04−3.10 (3H), 2.25 (1H), 2.01 (1H), 1.20 (3H); ^{13}C NMR δ 198.5, 156.3, 143.4, 139.8, 133.8, 132.9, 132.4, 128.8, 128.5, 128.2, 127.5, 126.8, 61.0, 54.8, 52.5, 28.1, 27.1, 14.5; IR (solid) $\upsilon_{\max}$ 3297, 3056, 2981, 2937, 2859, 1718, 1670, 1598, 1544, 1493, 1455, 1301, 1246, 1140, 1088, 1029 cm^{-1}. Anal. Calcd for C$_{20}$H$_{20}$NO$_3$Cl: C, 67.23; H, 5.60; N, 3.92. Found: C, 67.25; H, 5.62; N, 3.90.

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Note Added after ASAP Publication. The gold catalyst used throughout the paper and Supporting Information was incorrect in the version posted ASAP October 30, 2004; the corrected version was posted November 8, 2004.

Supporting Information Available: General experimental procedure and characterization data for new compounds **4a**, **4b**, and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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