Synthetic Methods

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# Dual Platinum and Pyrrolidine Catalysis in the Direct Alkylation of Allylic Alcohols: Selective Synthesis of Monoallylation Products**

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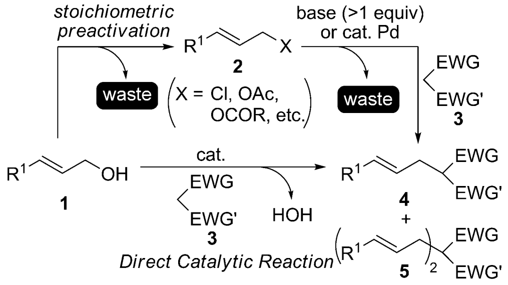
**Abstract:** *A dual platinum- and pyrrolidine-catalyzed direct allylic alkylation of allylic alcohols with various active methylene compounds to produce products with high monoallylation selectivity was developed. The use of pyrrolidine and acetic acid was essential, not only for preventing undesirable side reactions, but also for obtaining high monoallylation selectivity.*

The allylation of activated methylene compounds, such as 1,3-dicarbonyl compounds, is a very important carbon–carbon bond forming reaction because of the usefulness of the corresponding allylation products for the synthesis of natural and unnatural bioactive compounds.[1] As outlined in Scheme 1 (**1**→**2**→**4**), these transformations are generally achieved using allylic halides with more than equimolar amounts of base. Another synthetic method is the transition-metal-catalyzed substitution reaction of activated allylic alcohol derivatives, such as allylic halides, carboxylates, and carbonates, via a π-allylmetal intermediate, the so-called Tsuji–Trost reaction.[2] In these reactions, however, undesirable overreactions may occur to give the diallylated[3] compound **5**, and thus making it difficult to separate the desired monoallylation products from the reaction mixture. Although several highly mono-selective stoichiometric[4] and catalytic[5] reactions with some specific substrates have been reported, further development of mono-selective allylation with a broader substrate generality is in high demand.



***Scheme 1.*** Conventional two-step synthesis (**1**→**2**→**4**) and direct synthesis (**1**→**4**).

Direct catalytic substitution of underivatized allylic alcohols with carbon and heteroatom (N, O, and S) nucleophiles, which generated the desired allylated products together with water as the sole co-product, is a more straightforward and desirable method in terms of atom-economy and environmental concerns (Scheme 1, **1**→**4**).[6] Despite the poor leaving ability of the hydroxyl group, several palladium-[7,3c] and platinum-catalyzed[8] direct substitutions of allylic alcohols without the use of an activator were recently developed by various research groups, providing a highly atom-economical synthetic method for linear allylation products. In the case of carbon nucleophiles, however, Ozawa and Yoshifuji developed the only successful monoselective allylation by using unique π-allyl palladium complexes bearing bulky diphosphinidenecyclobutene (DPCB) ligands,[7a] but the substrate scope was limited.

We have previously demonstrated that a Pt catalyst system of [Pt(cod)$Cl_2$] and a ligand with a large bite angle, 2,2′-bis(diphenylphosphino)diphenyl ether (DPEphos) or 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), under microwave irradiation conditions promotes the direct catalytic amination of allylic alcohols with arylamines, alkylamines, and ammonia with high selectivity of the monoallylation products, where a sterically congested π-allyl Pt intermediate created by the large-bite-angle ligand allows for a preferential selective reaction with the substrate over the monoallylation compound.[8a–c] Herein, we report a dual platinum- and pyrrolidine-catalyzed allylic alkylation of both aryl- and alkyl-substituted allylic alcohols (18 examples) with various active methylene compounds (15 examples) and high monoallylation selectivity (92:8 to > 99:1). The addition of a catalytic amount of pyrrolidine and acetic acid is essential not only for preventing undesirable side reactions, but also for obtaining high monoallylation selectivity. Microwave irradiation efficiently accelerated the reaction without a loss of selectivity, making it possible to lower the reaction temperature to 60 °C and reduce the reaction time to 5 h. Based on several mechanistic investigations, we propose that pyrrolidine reacts with β-keto carbonyl compounds to generate enamines, which act as sterically more congested, but more reactive, nucleophiles.

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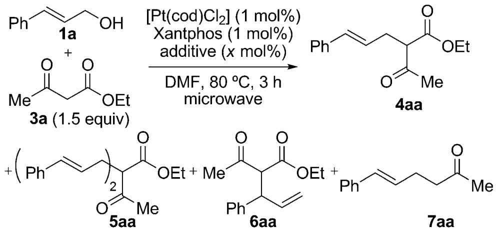
We began our study by evaluating efficient catalytic conditions using cinnamyl alcohol (**1a**) and ethyl acetoacetate (**3a**) as representative substrates. The reaction was first performed under the optimized reaction conditions for arylamine (Pt-Xantphos (1 mol%), DMF, 80°C, microwave irradiation), but the corresponding linear monoallylation product **4aa** was obtained in only 37% yield, along with several by-products, such as diallylation product **5aa**, branch monoallylation product **6aa**, and unexpected ketone product **7aa**; this last product could have been generated through transesterification and subsequent Pt-catalyzed decarboxylative allylation[9] (Table 1, entry 1). Because this undesirable transesterification could be catalyzed by hydrochloric acid generated in situ, we examined the addition of bases. As expected, the use of tertiary amines (entries 2 and 3), pyridine (entry 4), DBU (entry 5), and inorganic bases (entries 6 and 7) suppressed the formation of ketone **7aa**, but the yield of the monoallylation product remained lower than 40%, and a significant amount of the undesired diallylation product **5aa** and branch product **6aa** were obtained. To our surprise, the addition of pyrrolidine (50 mol%) not only completely suppressed the formation of **7aa**, but also greatly increased the monoallylation selectivity and regioselectivity, affording the desired product **4aa** in 82% yield (entry 8). Nearly identical results were obtained when proline was used instead of pyrrolidine (entry 9), but significant differences between them were observed when the amount of these additives was reduced to 10 mol%; the effect of pyrrolidine was remarkably diminished (entry 10), whereas the effect of proline was maintained (entry 11).

***Table 1:*** Additive effects on Pt-catalyzed direct alkylation with a β-ketoester.[a]



| Entry | Additive (*x* mol%) | Yield of **4aa** [%][b] | **4aa**/**5aa**[b] | Yield of **6aa** [%][b] | Yield of **7aa** [%][b] |
|---|---|---|---|---|---|
| 1 | none | 37 | 70:30 | 12 | 13 |
| 2 | $Et_3N$ (50) | 38 | 61:39 | 11 | n.d. |
| 3 | $Cy_2NEt$ (50) | 39 | 62:38 | 9 | n.d. |
| 4 | pyridine (50) | 32 | 60:40 | 9 | 7 |
| 5 | DBU (50) | 30 | 55:45 | 7 | n.d. |
| 6 | $K_2CO_3$ (50) | 28 | 55:45 | 4 | 8 |
| 7 | $NaHCO_3$ (50) | 37 | 60:40 | 6 | n.d. |
| 8 | pyrrolidine (50) | 82 | 92:8 | trace | n.d. |
| 9 | DL-proline (50) | 83 | 92:8 | trace | n.d. |
| 10 | pyrrolidine (10) | 50 | 72:28 | 8 | trace |
| 11 | DL-proline (10) | 84 | 93:7 | trace | n.d. |
| 12 | pyrrolidine (10)<br>$CH_3COOH$ (10) | 85 | 93:7 | trace | n.d. |
| 13 | $CH_3COOH$ (10) | 38 | 65:35 | 13 | 8 |
| 14[c] | pyrrolidine (10)<br>$CH_3COOH$ (10) | 89<br>85 [d] | 95:5 | trace | n.d. |
| 15[c,e] | pyrrolidine (10)<br>$CH_3COOH$ (10) | 83 | 91:9 | trace | n.d. |
| 16[f] | pyrrolidine (10)<br>$CH_3COOH$ (10) | 87 | 95:5 | trace | n.d. |
| 17[g] | pyrrolidine (10)<br>$CH_3COOH$ (10) | 82 [d] | 93:7 | trace | n.d. |

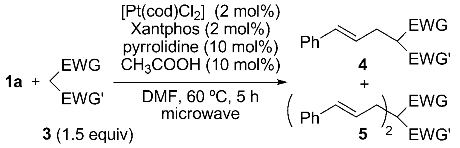
[a] 2.0 mmol scale, 0.4 mL of DMF was used. [b] Determined by $^1H$ NMR analysis of the crude reaction mixture. [c] 2 mol% of $[Pt(cod)Cl_2]$ and Xantphos was used. Reaction was performed at 60°C and 5 h microwave irradiation. [d] Yield of isolated product. [e] 1.0 equiv of **3a** was used. [f] 2 mol% of $[Pt(cod)Cl_2]$ and Xantphos was used. Reaction was performed by conventional heating at 70°C for 24 h. [g] 50 mmol (6.7 g of **1a**) scale using 0.5 mol% of $[Pt(cod)Cl_2]$ and Xantphos. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Cy = cyclohexyl, n.d. = not detected.

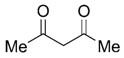
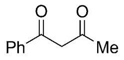
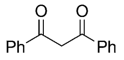
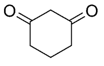
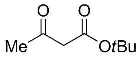
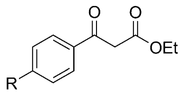
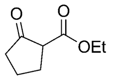
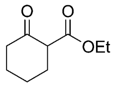
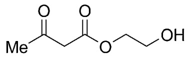
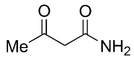
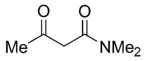
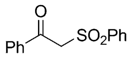
Identical results were achieved with pyrrolidine and proline when acetic acid (10 mol%) was added to the pyrrolidine system (entry 12). Without pyrrolidine, acetic acid exhibited no effect (entry 13). These results clearly indicate that both pyrrolidine and acetic acid are essential for the highly selective synthesis of **4aa**, and that these additives work independently. Under this dual co-catalyst system, the reaction temperature was reduced to 60°C (entry 14), and this was selected as the best condition for further investigation. Even when using just one equivalent of nucleophile **3a**, the reaction proceeded with high monoallylation selectivity (entry 15). Furthermore, conventional oil-bath heating was also applicable to this reaction (entry 16). Moreover, a gram-scale reaction using only 0.5 mol% of the Pt catalyst also proceeded smoothly (entry 17). Although proline and pyrrolidine have been used previously in reactions of the π-allyl palladium complex with ketone or aldehyde,[10] they have not been applied to reactions of activated methylene compounds, except for one example[10e] in which the use of 10 equivalents of nucleophile was required to obtain the monoallylation products.

With the optimized conditions in hand, we examined the scope of the active methylene compounds **3** (Table 2). Direct alkylation with 1,3-diketones (**3b**–**3d**) proceeded smoothly with high yield and high selectivity (entries 1–3). Notably, the reaction with cyclic 1,3-diketone **3e**, which has a highly acidic C−H group, also proceeded smoothly (entry 4). Several different β-keto esters were also applicable. When *tert*-butyl 3-oxobutanoate (**3f**) was used, the reaction proceeded without the decomposition of the *tert*-butyl ester (entry 5). The reaction with ethyl 3-oxo-3-phenylpropanoate (**3g**) and its derivatives with electron-donating (entries 7 and 8) and electron-withdrawing (entry 9) substituents proceeded smoothly to afford the corresponding monoallylation products **4ag**–**4aj** in good yield. The α-substituted active methylene compounds **3k** and **3l** were also applicable to the present catalysis (entries 10 and 11). The reaction with 2-hydroxyethyl 3-oxobutanoate (**3m**) proceeded with high yield and high selectivity (entry 12). Furthermore, reactions with β-ketoamides **3n** and **3o** (entries 13 and 14) and β-ketosulphone **3p** (entry 15) also proceeded to afford the corresponding monoallylation product **4an**–**4ap** in good to high yields.

We next examined the direct alkylation of various allylic alcohols **1** (Table 3). Direct alkylation of a series of cinnamyl alcohol derivatives, **1b**–**1i**, including the substrate with a highly acid-sensitive THP group **1g**, afforded the corresponding monoallylation products **4ba**–**4ia** with high yield

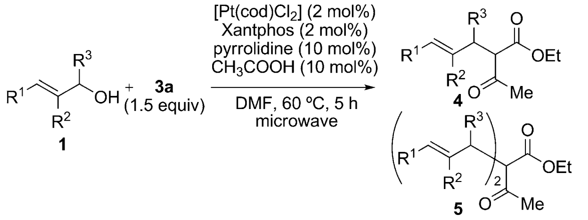
***Table 2:*** Pt-catalyzed direct alkylation of various active methyene compounds **3**.[a]

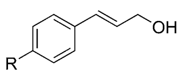
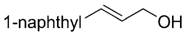
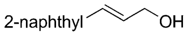
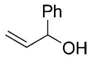
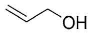
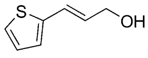
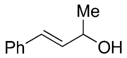
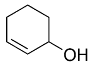
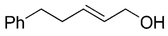
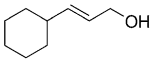
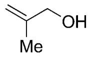
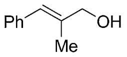


| Entry | Nucleophile | 3 | Yield of 4 [%][b] | 4/5[c] |
|---|---|---|---|---|
| 1 |  | **3b** | 82[d] | 93:7 |
| 2 |  | **3c** | 91 | >99:1 |
| 3[e] |  | **3d** | 87 | >99:1 |
| 4 |  | **3e** | 86 | 92:8 |
| 5[f] |  | **3f** | 83 | 95:5 |
| 6 |  | **3g** (R=H) | 88 | 97:3 |
| 7 |  | **3h** (R=OMe) | 91 | 97:3 |
| 8 |  | **3i** (R=NMe$_2$) | 88 | 97:3 |
| 9 |  | **3j** (R=CN) | 82 | 93:7 |
| 10[g] |  | **3k** | 85 | – |
| 11[g] |  | **3l** | 87 | – |
| 12 |  | **3m** | 83 | 95:5 |
| 13 |  | **3n** | 87 | 93:7 |
| 14 |  | **3o** | 93 | 97:3 |
| 15[e] |  | **3p** | 91 | >99:1 |

[a] 2.0 mmol scale, 0.4 mL of DMF was used. [b] Yield of isolated product. [c] Determined by $^1$H NMR analysis of the crude reaction mixture. [d] Product was a 1:1 mixture of keto and enol forms. [e] Reaction was performed at 80 °C. [f] 20 mol% of pyrrolidine was used. [g] Reaction was performed at 70 °C.

***Table 3:*** Pt-catalyzed direct alkylation of various allylic alcohols **1**.[a]



| Entry | Allylic alcohol | 1 | Yield of 4 [%][b] | 4/5[c] |
|---|---|---|---|---|
| 1 |  | **1a** (R=H) | 85 | 95:5 |
| 2 |  | **1b** (R=Me) | 81 | 92:8 |
| 3 |  | **1c** (R=Br) | 87 | 94:6 |
| 4 |  | **1d** (R=OMe) | 82 | 93:7 |
| 5 |  | **1e** (R=OH) | 83 | 97:3 |
| 6 |  | **1f** (R=OTBS) | 80 | 95:5 |
| 7 |  | **1g** (R=OTHP) | 84 | 96:4 |
| 8 |  | **1h** | 84 | 95:5 |
| 9 |  | **1i** | 82 | 95:5 |
| 10 |  | **1j** | 85[d] | 95:5 |
| 11 |  | **1k** | 86 | 93:7 |
| 12 |  | **1l** | 91 | 97:3 |
| 13[e] |  | **1m** | 80 | 97:3 |
| 14[e] |  | **1n** | 73 | 97:3 |
| 15[e] |  | **1o** | 78[f] | 96:4 |
| 16[e] |  | **1p** | 78 | 94:6 |
| 17[e,g] |  | **1q** | 77 | 92:8 |
| 18[e] |  | **1r** | 86[h] | 96:4 |

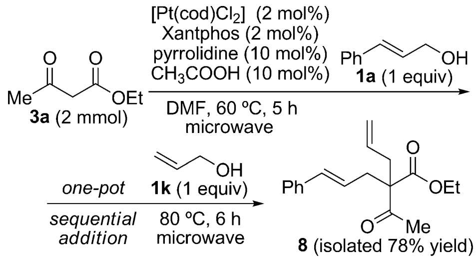
[a] 2.0 mmol scale, 0.4 mL of DMF was used. [b] Yield of isolated product. [c] Determined by $^1$H NMR analysis of the crude reaction mixture. [d] Linear product **4aa** was obtained. [e] 50 mol% each of pyrrolidine and acetic acid was used. [f] A 2.4:1 *E*/*Z* mixture was obtained. [g] Reaction was performed at 80 °C. [h] A 2.8:1 *E*/*Z* mixture was obtained. TBS = *tert*-butylsilyl, THP = tetrahydropyranyl.

and high selectivity (entries 2–9). Notably, the branched allylic alcohol **1j** was efficiently converted into the linear monoallylation product **4aa** with the same **4**/**5** ratio (entry 10) as in the reaction of **1a** (entry 1). The reaction of allyl alcohol (**1k**) also proceeded (entry 11) similarly to the reactions of cinnamyl alcohol derivatives **1a**–**1g**.

Furthermore, highly unstable thiophene-substituted allylic alcohol **1l** was successfully converted into the corresponding monoallylation product **4la** without decomposition (entry 12). Alkyl-substituted allylic alcohols have the potential risk of β-hydride elimination. For reactions with **1m**–**1r**, we obtained good yield and high selectivity by using 50 mol% of both pyrrolidine and acetic acid to enhance the reactivity by increasing the enamine intermediates. Even when using the less-reactive β-substituted allylic alcohols **1q** and **1r**, good yields were obtained under these conditions. To the best of our knowledge, this is the first report of such broad substrate generality (both aryl- and alkyl-substituted allylic alcohols and several active methylene compounds) and such high monoallylation selectivity in this type of direct reaction.

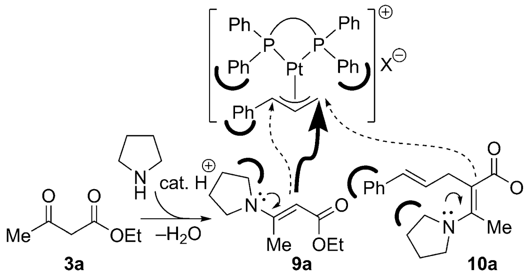
Development of the present highly monoselective allylation allowed for a one-pot sequential allylation of two different allylic alcohols, **1a** and **1k**, with active methylene compound **3a** to provide dissymmetric diallylated compound **8** containing different allyl moieties in 78% yield (Scheme 2). Thus, this new method could provide increased flexibility for designing a synthetic route.

To gain insight into the effects of pyrrolidine and acetic acid, we performed the following controlled reactions. Direct



*Scheme 2.* One-pot synthesis of diallylated compound **8** with two different allyl moieties from active methylene compound **3a**.

alkylation of **1a** with enamine **9a** produced results identical to those of the reaction of β-keto ester **3a** in the presence of catalytic amounts of pyrrolidine and acetic acid.[11] Moreover, direct alkylation with the mixture of **3a** and a catalytic amount of **9a** and acetic acid also produced almost the same result. On the other hand, the use of *N*-methylpyrrolidine instead of pyrrolidine gave a mixture of **4aa**, **5aa**, and **6aa**. These results strongly suggest that pyrrolidine acts as an organocatalyst to form the enamine intermediate **9**, which then reacts with the π-allyl platinum complex generated in situ (Scheme 3). The above-mentioned byproducts were not formed due to the steric effects of the bulkier enamine nucleophile **9** (compared with β-keto ester **3**). In the absence of acetic acid, both the yield of the product and the monoallylation selectivity were highly dependant on the amount of pyrrolidine present. In addition, when enamine **9** was used as the carbon nucleophile instead of **3**, the reaction efficiently proceeded, even in the absence of acetic acid. The results suggested that acetic acid promotes the generation of enamine **9** by activating the carbonyl group of the active methylene compound **3**.[11] The use of L-proline instead of the combination of pyrrolidine and acetic acid has only thus far given racemic products.[10,11]



*Scheme 3.* Proposed effects of pyrrolidine and acetic acid.

In summary, we have developed a highly monoallylation-selective direct alkylation of allylic alcohols with broad substrate generality promoted by dual platinum–Xantphos and pyrrolidine catalysis. The use of pyrrolidine was essential for obtaining monoallylation selectivity, and mechanistic studies revealed that this catalysis proceeded through an enamine intermediate. Moreover, this catalytic system allows for easy synthesis of diallylation compounds with two different allyl groups. Further mechanistic studies, further investigation of the scope of the syntheses of highly functionalized bioactive compounds, and application to enantioselective variants are ongoing in our group.

## Experimental Section

Cinnamyl alcohol **1a** (268 mg, 2.0 mmol, 1.0 equiv), ethyl acetoacetate **3a** (390 mg, 3.0 mmol, 1.5 equiv), acetic acid (12 mg, 0.2 mmol, 10 mol%) and pyrrolidine (14 mg, 0.2 mmol, 10 mol%) were added to a solution of [Pt(cod)Cl$_2$] (15.0 mg, 0.04 mmol, 2 mol%) and Xantphos (23.2 mg, 0.04 mmol, 2 mol%) in DMF (0.4 mL). The reaction was heated at 60°C using a CEM Discover single-mode microwave reactor (standard mode) for 5 h. The selectivity was determined by the $^1$H NMR spectrum of the crude reaction mixture. The mixture was purified using *n*-hexane/ethyl acetate (20:1–3:1) as eluent to give **4aa** as a colorless oil (419.4 mg, 85% yield).

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[11] See the Supporting Information for details.