

Development of Transition Metal-catalyzed Direct and Chemoselective Alkylation Reactions

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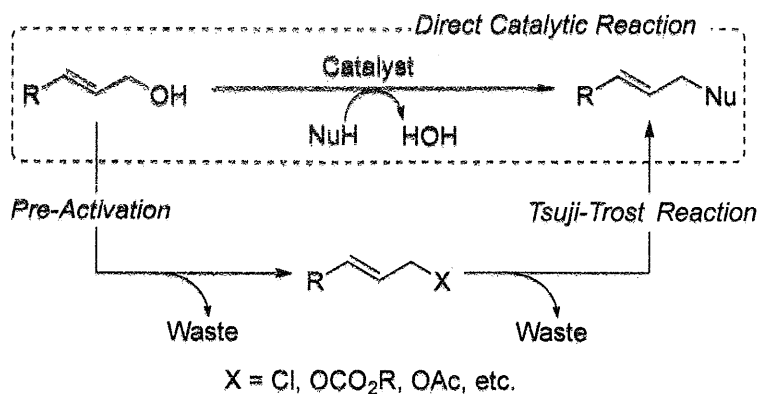
遷移金属触媒を用いた直接的と化学選択的置換反応の開発

環境調和創薬化学分野 3PS14028T 林璐

【Introduction】

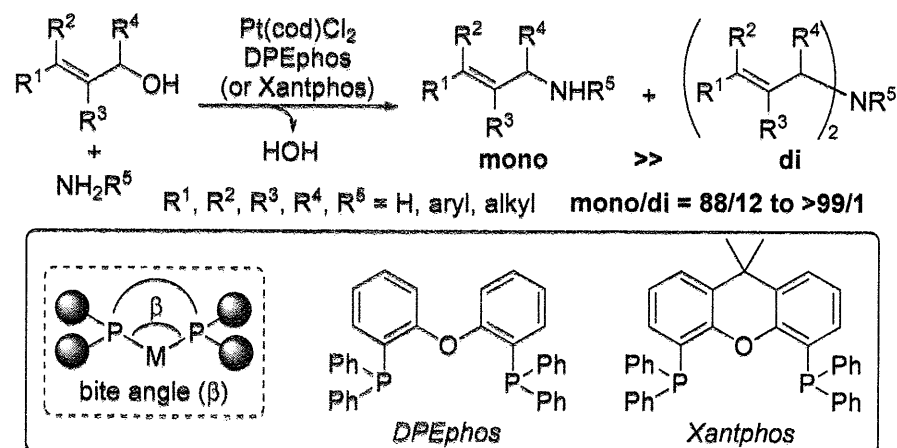
The allyl group is widely encountered in organic and pharmaceutical chemistry. It could work as a crucial structure of natural and unnatural compounds, which may possess various biological function or could work as a precursor in synthesizing these compounds. In order to introduce allyl group into compounds, allylic alcohols would be ideal allylating agents because of their availability and stability. Due to the poor leaving ability of hydroxyl group, however allylic alcohols should be pre-activated into other activated substrates such as allyl halides, carbonates and acetates, followed by Tsuji-Trost reaction to afford the desired compounds. In these synthesizing procedure, more than stoichiometric amount of unwanted waste are produced during both pre-activation and Tsuji-Trost reaction. Thus, a direct catalytic substitution of allylic alcohols, which forms water as the sole coproduct, has recently attracted much attention from an environmental and atom-economical point of view (Scheme A-1).

Scheme A-1 Direct Catalytic Reaction



Our group is also working on the direct catalytic substitution of allylic alcohols without pre-activation, by the function of Pt catalyst and large bite angle ligand DPEphos or Xantphos, the amination of allylic alcohols was occurred with aromatic amine and aliphatic amine or even ammonia solution. And in these reactions, high mono-selectivity was obtained, which is difficult to realize in conventional methods (Scheme A-2)¹.

Scheme A-2 Our Previous Work



To dig the investigation deeper, we developed the research of direct mono-selective alkylation of allylic alcohols via Platinum-pyrrolidine catalytic system and also chemoselective substitution between different electrophiles via transition metal.

【Contents】

1. The Development of Direct Mono-selective Alkylation of Allylic Alcohols via Platinum-Pyrrolidine Catalytic System

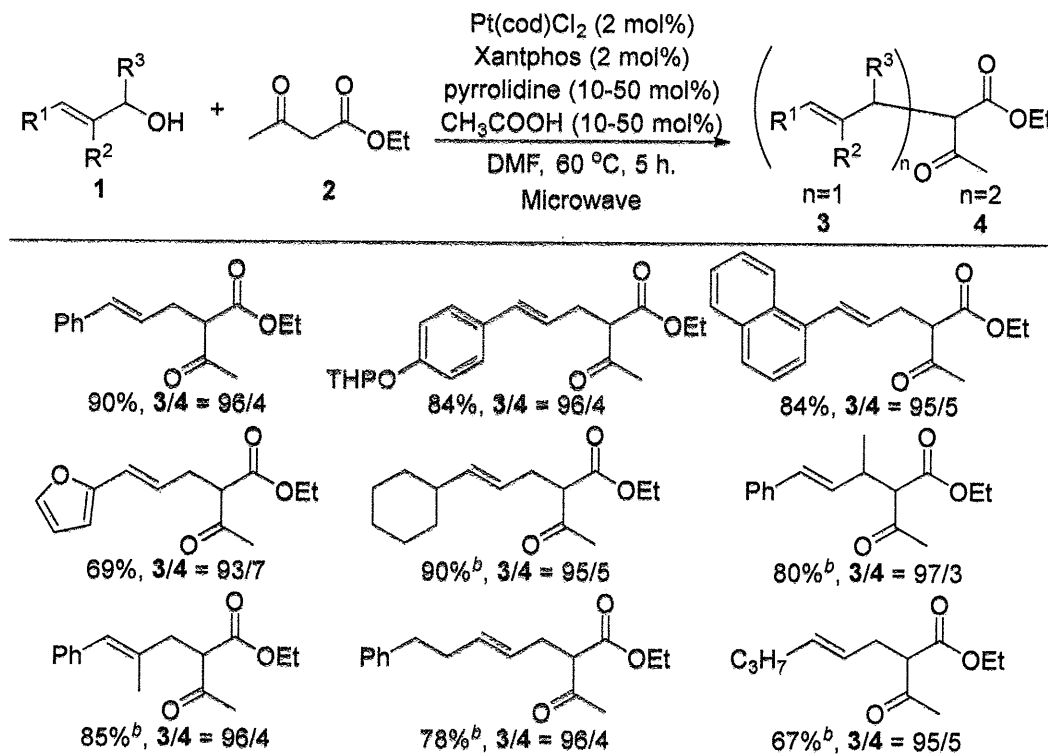
[Purpose]

The allylation of activated methylene compounds has attract many researchers' attention during recent years. But the existence of di-allylation compounds produced from overreaction perplexed the researchers. So we focused on the direct mono-selective alkylation of allylic alcohols by former catalytic system².

[Method and Result]

From the report of Dr. Shibuya in our research group³, byproducts were suppressed by adding acetic acid and pyrrolidine, thus the mono-selective alkylation of allylic alcohols was achieved in high yield and high selectivity. With this optimized condition in hand, I explored the substrate scope, both aromatic alcohols and aliphatic alcohols lead to good yield, also acid sensitive group, fused rings and heterocycle tolerant well (Scheme A-3).

Scheme A-3^a Direct Mono-selective Alkylation of Allylic Alcohols



^a 2.0 mmol scale, 0.4 mL DMF was used, yield is isolated yield and the 3/4 ratio is determined by ¹H NMR analysis. ^b 50 mol% of pyrrolidine and 50 mol% of CH_3COOH was used.

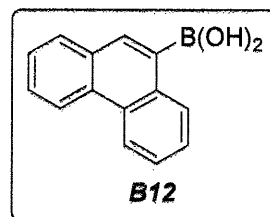
2. The Development of Chemoselective Substitution via Transition Metal between Allylic Alcohols and Allylic Amines as Electrophiles

[Purpose]

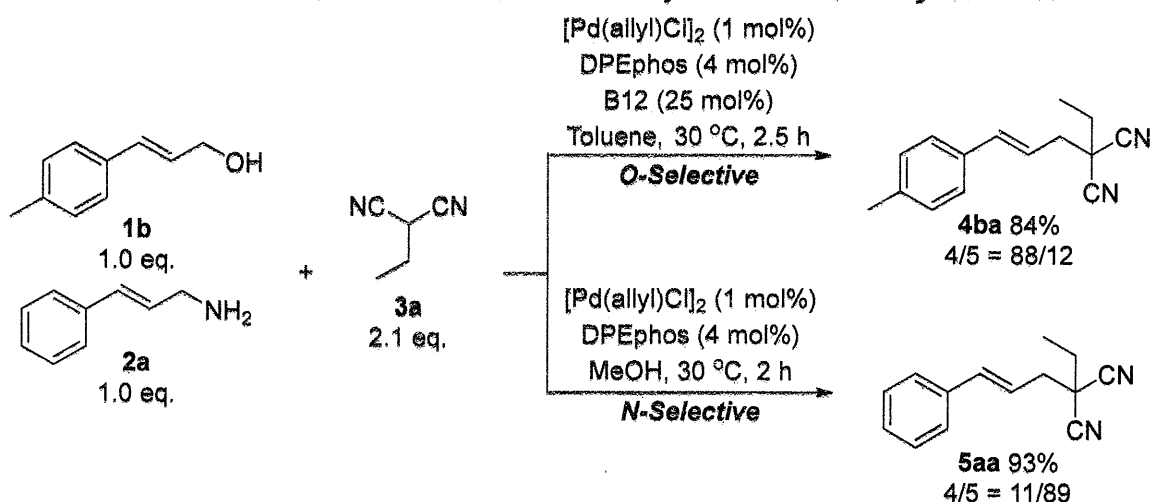
Chemoselectivity describes the preferential reaction of a given reagent with one of two or more functional groups that are present in a reactant or a group of reactants. Our group reported chemoselective reactions between two different nucleophiles⁴, but chemoselectivity between different electrophiles has not been studied. On the other hand, just like allylic alcohols, allylic amine is seldom used in Tsuji-Trost reaction due to the poor leaving ability of amino group. So, combine the study reported above, I focused on the chemoselective substitution between allylic alcohols and allylic amines as electrophiles. This means under one condition, only allylic alcohols proceed the substitution, and under the other condition, only allylic amines proceed the substitution.

[Method and Result]

Between allylic alcohol **1b**, allylic amine **2a** and nucleophile **3a**, the chemoselective reactions were examined (Scheme A-4)⁵. Under the function of palladium catalyst, 84% yield and 88/12 alcohol selectivity was obtained with the existence of activator boronic acid **B12**, and 93% yield and 89/11 amine selectivity was achieved by the activation of solvent MeOH. Aromatic alcohols and amines including fused rings and heterocycles lead to very good yield and selectivity. Aliphatic alcohols and amines show some difficulties on achieving high yield and selectivity.



Scheme A-4 chemoselective Substitution between Allylic Alcohols and Allylic Amines



[Reference]

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