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Highly Efficient and Regioselective Allylation with Allylic Alcohols Catalyzed by [$Mo_3S_4Pd(\eta^3$-allyl)] Clusters

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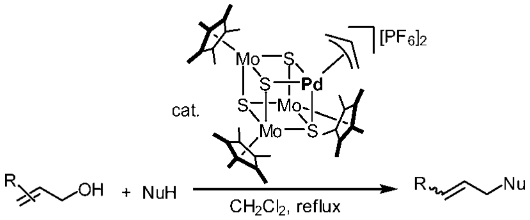
ABSTRACT



A highly efficient and regioselective allylation reaction of amines and active methylene compounds directly using allylic alcohols under mild conditions catalyzed by the novel cubane-type sulfido [$(Cp^*Mo)_3(\mu_3\text{-}S)_4Pd(\eta^3$-allyl)][$PF_6$]$_2$ clusters has been developed. A variety of allylic alcohols and nucleophiles including amines and active methylene compounds are investigated, and in the case of allylic alcohols bearing substituents at either the α- or γ-position only linear products are obtained.

Palladium-catalyzed allylic alkylations are important C−C and C−heteroatom bond formation reactions with many applications in organic synthesis.[1] Most frequently, allyl acetates and carbonates have been used as electrophiles in these reactions, while from an economical and environmental point of view, the direct use of allylic alcohols is more profitable for two reasons.[2] One is that the reaction of allylic alcohols forms water as a coproduct, whereas allylic halides and esters afford corresponding salt wastes under basic conditions. The other is that allylic acetates and carbonates are derivatives of allylic alcohol, and using allylic alcohols directly can avoid redundant synthetic steps. To cleave the inert C−O bond of allylic alcohol, some Lewis acids were used, such as As_2O_3,[3] B_2O_3,[4] BPh_3,[5] BEt_3,[6] $SnCl_2$,[7] CO_2,[8] $Ti(O^iPr)_4$,[9] $Nb(OEt)_5$,[10] carboxylic acid,[11] and so on. Due to the weak leaving capability for the OH group, successful application of allylic alcohols without any activating reagents is less reported.[12]

Ozawa and co-workers reported (η^3-allyl)palladium complexes bearing diphosphinidenecyclobutene ligand (DPCB) catalyzed allylation of aniline and active methylene

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(1) For recent reviews, see: (a) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258, and references cited therein. (b) Tsuji, J. In *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; John Wiley & Sons, Ltd.: Chichester, U.K., 2004; Chapter 4, p 431. (c) Trost, B. M.; Vranken, D. L. V. *Chem. Rev.* **1996**, *96*, 395. (d) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

(2) For recent reviews on allylation reaction of allylic alcohols, see: (a) Muzart, J. *Eur. J. Org. Chem.* **2007**, 3077, and references cited therein. (b) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647.

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(4) Lu, X.; Jian, X.; Tao, X. *J. Organomet. Chem.* **1998**, *344*, 109.

(5) Stary, I.; Stara, I. G.; Kocovsky, P. *Tetrahedron Lett.* **1993**, *34*, 179.

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(9) (a) Satoh, T.; Ikeda, M.; Miura, M; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4877. (b) Yang, S.; Hung, C. *J. Org. Chem.* **1999**, *64*, 5000. (c) Yang, S.; Tsai, Y. *Organometallics* **2001**, *20*, 763.

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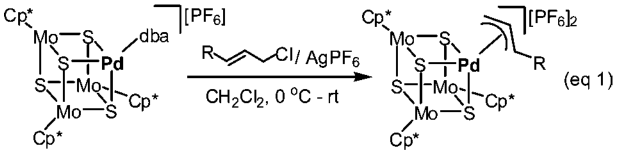
10.1021/ol100805c

compounds.[12b] Le Floch's group tested the performance of a range of cationic palladium complexes bearing mono- or bidentate phosphane ligands and found $[(\eta^3\text{-allyl})PdL_2][NTf_2]$ (L = 1,2,5-triphenylphosphole, Tf = SO_2CF_3) was the best catalyst for allylation with allyl alcohol.[12e] Recently, self-assembling palladium phosphane catalysts were applied in the allylation of *N*-heterocycles with allylic alcohols.[12g] Although cationic palladium complexes incorporating the π-allyl ligand have high catalytic activity, in the allylic alkylation reaction, the regioselectivity is decreased due to the formation of both linear and branched products.[12b,e,g]

Owing to novel structures and unique catalytic activities, metal−sulfur cubane-type clusters have drawn much attention.[13] Very recently we reported[14] a highly efficient and regioselective allylation reaction of amines with allylic alcohols under mild conditions catalyzed by $[(Cp^*Mo)_3(\mu_3\text{-}S)_4Pd(dba)][PF_6]$[15] ($Cp^* = \eta^5\text{-}C_5Me_5$; dba = dibenzylideneacetone) with H_3BO_3 as an additive, and only linear products were obtained by this catalytic system. Herein, our extended study found that novel cubane-type sulfido clusters $[Mo_3S_4Pd(\eta^3\text{-allyl})]$ with η^3-allyl ligands showed highly efficient catalytic activity for the allylation reaction with allylic alcohols without any additives under mild conditions.

Complexes $[(Cp^*Mo)_3(\mu_3\text{-}S)_4Pd(\eta^3\text{-}C_3H_4R)][PF_6]_2$ (**1a**, R = H; **1b**, R = Ph) were synthesized by treating $[(Cp^*Mo)_3(\mu_3\text{-}S)_4Pd(dba)][PF_6]$ (**2**) with corresponding allylic halides and $AgPF_6$ in CH_2Cl_2 from 0 °C to room temperature and isolated as yellowish green solids in 90 and 71% yields, respectively (eq 1). Figure 1 shows the molecular structure of **1a**. The $(Cp^*Mo)_3S_4$ chelates the $(\eta^3\text{-allyl})$palladium moiety through three sulfur atoms. The bond length of Pd−C31 is similar to Pd−C33. C31−C32 and C32−C33 bond lengths (1.389(16) and 1.401(15) Å) and the C31−C32−C33 angle (115.8(11) °) are in the typical ranges for η^3-allyl ligands.

The allylation of *N*-methylaniline (**4a**) with allyl alcohol (**3a**) was chosen as a model reaction to study the catalytic activity of **1** and other Pd complexes (eq 2). The results are summarized in Table 1. In the presence of 5 mol % catalyst, general Pd complexes (entries 1−4) have no or low activity for this allylation reaction in CH_2Cl_2 under reflux conditions.



2

1a, R = H, 90%; **1b**, R = Ph, 71%

Neither the incomplete cubane-type cluster[15] (entry 5) nor the cubane-type sulfido cluster $[Mo_3PdS_4]$ bearing dba or PPh_3 ligand[15] (entries 6−7) could catalyze this reaction.

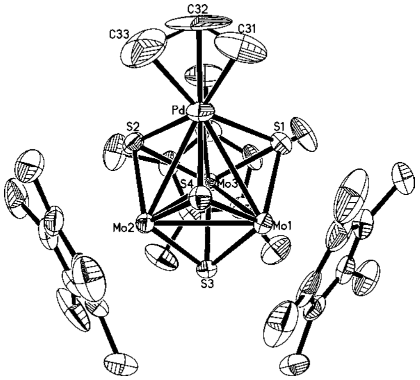
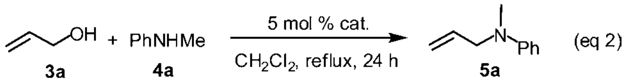


Figure 1. ORTEP representation of the molecular structure of **1a** with 30% probability ellipsoids. Hydrogen atoms and the PF_6^- ion are omitted for clarity. Selected bond distances (Å) and angles (deg): Pd−C31 2.124(11), Pd−C32 2.102(9), Pd−C33 2.183(10), C31−C32 1.389(16), C32−C33 1.401(15); C32−C31−Pd 70.0(6), C33−C32−Pd 74.1(6), C31−C32−C33 115.8(11).

To our delight, we found **1a** could smoothly catalyze allylation of *N*-methylaniline by directly using allyl alcohol without any additives and 96% yield was obtained in 24 h

Table 1. Catalytic Activity of Pd Complexes and Cubane-Type Sulfido Clusters[a]



3a **4a** **5a**

entry	cat.	yield[b] (%)
1	$PdCl_2$	0
2	$PdCl_2(PPh_3)_2$	0
3	$Pd(dba)_2$	0
4	$Pd(PPh_3)_4$	32
5	$[(Cp^*Mo)_3(\mu_2\text{-}S)_3(\mu_3\text{-}S)][PF_6]$	0
6	$[(Cp^*Mo)_3(\mu_3\text{-}S)_4Pd(dba)[PF_6]$ (**2**)	0
7	$[(Cp^*Mo)_3(\mu_3\text{-}S)_4Pd(PPh_3)][PF_6]$	0
8	$[(Cp^*Mo)_3(\mu_3\text{-}S)_4Pd(\eta^3\text{-}C_3H_5)][PF_6]_2$ (**1a**)	96 (94)[c]
9	$[(Cp^*Mo)_3(\mu_3\text{-}S)_4Pd(\eta^3\text{-}C_3H_4Ph)][PF_6]_2$ (**1b**)	90

[a] Reaction conditions: cat. 0.02 mmol, *N*-methylaniline 0.4 mmol, allyl alcohol 0.4 mmol, CH_2Cl_2 1 mL, reflux, 24 h. [b] Determined by GC with naphthalene as an internal standard. [c] Isolated yield.

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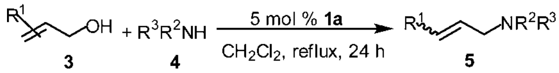
(12) For Pd-catalyzed direct allylation reactions of allylic alcohols, see: (a) Qu, J.; Ishimura, Y.; Nagato, N. *Nippon Kagaku Kaishi* **1996**, 787. (b) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968. (c) Liang, H.; Ito, S.; Yoshifuji, M. *Org. Lett.* **2004**, *6*, 425. (d) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 2595. (e) Thoumazet, C.; Grutzmacher, H.; Deschamps, B.; Ricard, L.; Le Floch, P. *Eur. J. Inorg. Chem.* **2006**, 3911. (f) Mora, G.; Deschamps, B.; van Zutphen, S.; Le Goff, X. F.; Richard, L.; Le Floch, P. *Organometallics* **2007**, *26*, 1846. (g) Usui, I.; Schmidt, S.; Keller, M.; Breit, B. *Org. Lett.* **2008**, *10*, 1207.

(13) For recent reviews, see: (a) Hidai, M.; Kuwata, S. *Acc. Chem. Res.* **2000**, *33*, 46. (b) Hernandez-Molina, R.; Sokolov, M. N.; Sykes, A. G. *Acc. Chem. Res.* **2001**, *34*, 223. For catalytic activity of metal−sulfur cubane-type clusters, see: (c) Murata, T.; Mizobe, Y.; Gao, H.; Ishii, Y.; Wakabayashi, T.; Nakano, F.; Tanase, T.; Yano, S.; Hidai, M.; Echizen, I.; Nanikawa, H.; Motomura, S. *J. Am. Chem. Soc.* **1994**, *116*, 3389. (d) Wakabayashi, T.; Ishii, Y.; Ishikawa, K.; Hidai, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2123. (e) Takei, I.; Wakebe, Y.; Suzuki, K.; Enta, Y.; Suzuki, T.; Mizobe, Y.; Hidai, M. *Organometallics* **2003**, *22*, 4639. (f) Takei, I.; Enta, Y.; Wakebe, Y.; Suzuki, T.; Hidai, M. *Chem. Lett.* **2006**, *35*, 590. (g) Feliz, M.; Guillamon, E.; Llusar, R.; Vicent, C.; Stiriba, S.; Perez-Prieto, J.; Barberis, M. *Chem.−Eur. J.* **2006**, *12*, 1486.

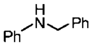
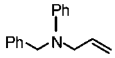
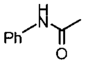
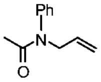
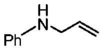
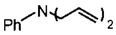
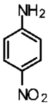
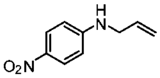
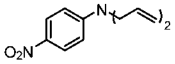
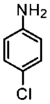
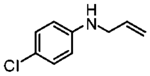
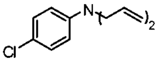
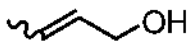
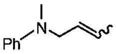
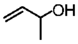
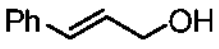
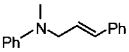
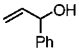
(14) Tao, Y.; Zhou, Y.; Qu, J.; Hidai, M. *Tetrahedron Lett.* **2010**, *51*, 1982.

(entry 8). Compound **1b** exhibited comparable catalytic activity with **1a** (entry 9) and gave 90% yield of product.

Table 2. Allylation of Amines with Allylic Alcohols Catalyzed by **1a**^{a}



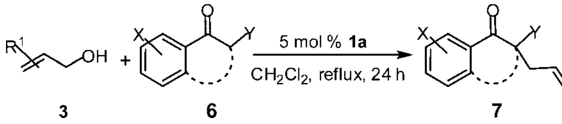
(eq 3)

entry	3	4	product	yield^{b} (%)
1	**3a**	 **4b**	 **5b**	91
2	**3a**	 **4c**	 **5c**	61
3	**3a**	$PhNH_2$ **4d**	 **5da**  **5db**	53 22^{c}
4	**3a**	 **4e**	 **5ea**  **5eb**	58 19^{c}
5	**3a**	 **4f**	 **5fa**  **5fb**	53 22^{c}
6	 **3b**	**4a**	 **5g**	95^{d}
7	 **3c**	**4a**	**5g**	91^{e}
8	 **3d**	**4a**	 **5h**	95
9	 **3e**	**4a**	**5h**	92

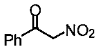
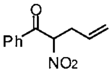
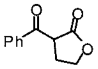
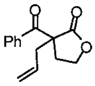
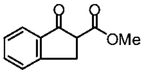
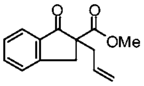
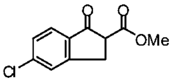
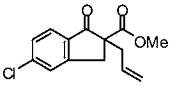
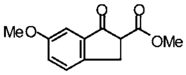
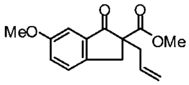
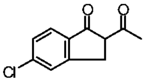
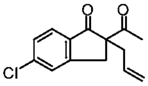
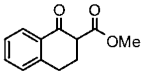
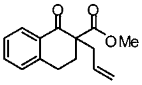
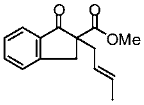
^{a} Reaction conditions: **1a** 0.02 mmol, amine 0.4 mmol, allylic alcohol 0.4 mmol, CH_2Cl_2 1 mL, reflux, 24 h. ^{b} Isolated yield. ^{c} Yield based on anilines. ^{d} *E*/*Z* = 5.8:1. ^{e} *E*/*Z* = 5.1:1.

We chose **1a** as the catalyst and investigated the reactions of a series of amines and allylic alcohols for activity and regioselectivity (Table 2). Besides **4a**, the other secondary amine, **4b**, was also examined and good yield was obtained (entry 1). Acetanilide (**4c**), which has lower nucleophilicity than **4a**, also gave good yield (entry 2). For the primary amines, when equivalence of aniline and allyl alcohol were applied, both mono- and diallylation products were obtained and the mole ratio was 71:29. Other *para*-substituted aniline derivatives with Cl and NO_2 groups underwent the allylation reaction smoothly to afford corresponding mono- and diallylation products, respectively. The ratio of products is similar to **4d** (entries 4 and 5).

Table 3. Allylation of Active Methylene Compounds with Allylic Alcohols Catalyzed by **1a**^{a}



(eq 4)

entry	3	6	product	yield^{b} (%)
1	**3a**	 **6a**	 **7a**	83
2	**3a**	 **6b**	 **7b**	47
3	**3a**	 **6c**	 **7c**	94
4	**3a**	 **6d**	 **7d**	98
5	**3a**	 **6e**	 **7e**	96
6	**3a**	 **6f**	 **7f**	95
7	**3a**	 **6g**	 **7g**	97
8	**3b**	**6c**	 **7h**	82
9	**3c**	**6c**	**7h**	70

^{a} Reaction conditions: **1a** 0.02 mmol, active methylene compound 0.4 mmol, allylic alcohol 0.4 mmol, CH_2Cl_2 1 mL, reflux, 24 h. ^{b} Isolated yield.

The reactions of allylic alcohols bearing a methyl or phenyl substituent at either the α- or γ- position were examined. Both crotyl alcohol and 3-butene-2-ol (entries 6 and 7) reacted with **4a** to produce **5g** without any detection of branched products. Cinnamyl alcohol and α-vinylbenzyl alcohol as substrates also gave good yield and only the *E* product **5h**. These results apparently indicated that this reaction proceeded via a common π-allylpalladium intermediate.

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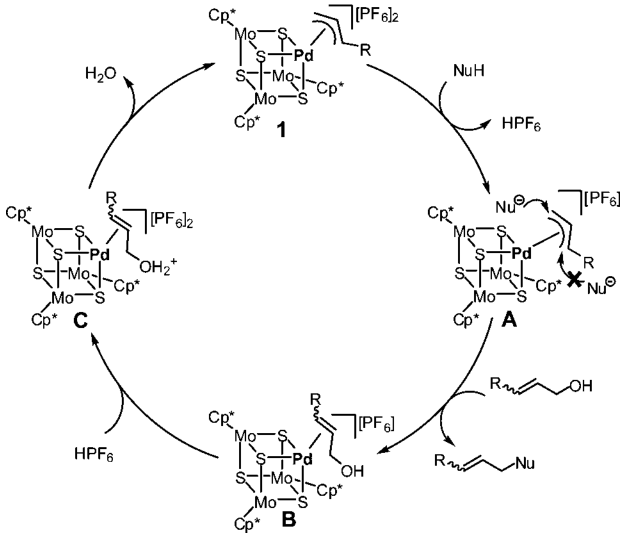
(15) Takei, I.; Suzuki, K.; Enta, Y.; Dohki, K.; Suzuki, T.; Mizobe, Y.; Hidai, M. *Organometallics* **2003**, *22*, 1790.

Scheme 1. Proposed Mechanism for Allylation Reaction



Encouraged by this result, we further investigated the allylation reaction of active methylene compounds with allylic alcohol (Table 3). 2-Nitro-1-phenylethanone (**6a**) as nucleophile could smoothly react with **3a** to produce monoallylation product **7a** in 83% yield. 3-Benzoyl-dihydrofuran-2-one (**6b**) reacted with allyl alcohol affording moderate yield. In this catalytic system, 2-carboxylsubstituted-1-indanone or 1-tetralone compounds also reacted with allyl alcohol to give corresponding products in high yield (entries 3−7). Substituents in phenyl did not affect the catalytic activity. To our surprise, different from the mixture *Z* and *E* produts of **5g**, the reaction of **3b** and **3c** with **6c** gave only **7h** with *E* configuration.

The proposed mechanism of this catalytic reaction was shown in Scheme 1. Proton produced by nucleophilic attack of nucleophile to **1** promoted the C−O bond cleavage of allylic alcohol. This process is analogous to Pd- or Ru-catalyzed allylation reaction reported by Le Floch[16] and Pregosin's[17] group, respectively. The regeoselectivity is ascribed to the nucleophilic attack of nucleophile to the less hindered allyl carbon in **A** (Scheme 1).

In summary, under mild conditions, a highly efficient and regioselective allylation reaction of amines and active methylene compounds directly using allylic alcohols catalyzed by novel $[(Cp^*Mo)_3(\mu_3\text{-}S)_4Pd(\eta^3\text{-}C_3H_4R)][PF_6]_2$ (R = H, Ph) complexes has been described. A variety of allylic alcohols and nucleophiles were investigated. The reaction proceeded with excellent regioselectivity, leading to a linear product for allylic alchols bearing substituents at either the α- or γ-position.

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

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(16) Piechaczyk, O.; Thoumazet, C.; Jean, Y.; Le Floch, P. *J. Am. Chem. Soc.* **2006**, *128*, 14306.

(17) Zaitsev, A. B.; Gruber, S.; Pregosin, P. S. *Chem. Commun.* **2007**, 4692.