Rhodium Catalyzed 1,4-Conjugate Addition of 1,5-Azastibocines with Electron Deficient Olefins

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The rhodium-catalyzed reaction of *Sb*-aryl-1,5-azastibocines with α,β-unsaturated ketones and esters is described. Exclusive formation of 1,4-conjugate adduct was achieved in aqueous NMP (*N*-methyl-2-pyrrolidinone) in the presence of 5 mol% of $[RhCl(cod)]_2$, and no formation of Heck adduct was observed in this condition. Reactions with various enones and enoates were also demonstrated to prove generality of the 1,4-conjugate addition.

Key words 1,5-azastibocine; 1,4-conjugate addition; rhodium catalyst; organoantimony compound; main group element; aqueous solvent

Recent advances of metal catalyzed C–C bond formation are remarkable,[1] as a result of the development of sophisticated ligands of transition metals,[2] elaboration of effective transmetallating agents,[3] employment of ionic liquids as reaction medium,[4] and microwave technology.[5] Especially, research on effective transmetallating agents is a field of attention. With these agents, the transition metal-catalyzed reactions can be carried out efficiently under mild conditions and the reactions become applicable to unstable compounds with labile functional groups.

Progress in chemistry of main group elements[6] contributes much to the development of efficient transmetallating agents because main group compounds exhibit suitable properties for the metal catalyzed reaction. Particularly, heavier element compounds below third low show soft nucleophilic characteristics, and are considered to be reasonable partners for soft electrophiles such as α,β-unsaturated carbonyl compounds.

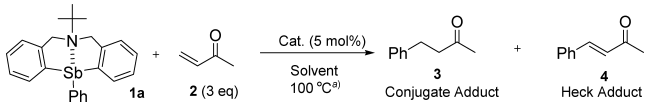
For 1,4-conjugate addition, one of the most conventional and prevailing methods is the use of soft copper reagents such as organocuprates.[7] However, because these reagents have to be prepared from moisture sensitive organolithiums,[8] Grignard reagents,[9] and organozinc reagents,[10] the reactions have to be carried out in strict anhydrous conditions under an inert atmosphere.

Another method for 1,4-conjugate addition was pioneered by Miyaura and co-workers using boronic acid in the presence of rhodium catalysts.[11] Inspired by this work, a number of main group compounds were investigated for the transition metal catalyzed 1,4-conjugate addition including organo-aluminum,[12] -boron,[13] -tin,[14] -silicon,[15] -bismuth,[16] -indium,[17] -plumbum,[18] -zirconium[19] and -zinc[20] compounds. Unlike copper reagents, these compounds exhibit a tolerance for hard electrophiles such as water and the reactions can be carried out in an aqueous medium.

Over the past few years, we have investigated the chemistry of organoantimony compounds and revealed that 1,5-azastibocines (**1**) with N–Sb intramolecular interaction are excellent transmetallating agents in Pd-catalyzed cross-coupling reactions.[21,22] These results prompted us to investigate 1,4-conjugate addition using 1,5-azastibocines (**1**) with an expectation of mild reaction conditions in aqueous media.

First, various transition metal catalysts were investigated for the reaction of *Sb*-phenyl-1,5-azastibocines (**1a**) with methyl vinyl ketone (**2**) in 1,4-dioxane : H_2O (10 : 1). The reaction mixture was heated at 100 °C under an argon atmosphere until almost all the starting material was consumed. In the presence of 5 mol% of palladium catalysts, none of the conjugate adduct (**3**) was observed and only Heck-type product (**4**) was formed (Table 1, entries 1—3). Nickel catalysts are reported to be effective for indium-mediated 1,4-conjugate addition,[23] however, neither $NiCl_2(PPh_3)_2$ nor $Ni(cod)_2$ promoted the reaction of 1,5-azastibocine (**1a**) with methyl vinyl ketone (**2**) and all the starting stibocine (**1a**) was recov-

Table 1. Investigation of Catalyst and Solvent



Entry	Catalyst	Solvent	Time (h)	**3** (%)[b)]	**4** (%)[b)]
1	$Pd(OAc)_2$	Dioxane : H_2O (10 : 1)	24	—	79
2	$PdCl_2$		24	—	43
3	$PdCl_2(PPh_3)_2$		24	—	14
4	$Rh(acac)(C_2H_4)_2$		24	36	36
5	$Rh(nbd)ClO_4$		16	55	11
6	$Rh(cod)BF_4$		14	78	—
7	$[Rh(OH)(cod)]_2$		16	80	11
8	$[RhCl(cod)]_2$		9	81	—
9	$[RhCl(cod)]_2$	THF : H_2O (10 : 1)	5.5	70	—
10		DME : H_2O (10 : 1)	3.5	84	—
11		C_2H_5OH	1	75	—
12		DMU : H_2O (10 : 1)	1	76	6
13		TMU : H_2O (10 : 1)	2.5	77	—
14		NMP : H_2O (10 : 1)	1	83	—
15		NMP	1	74	9

a) Oil bath temperature. *b*) Isolated yield.

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ered unchanged. Under the rhodium catalysts (5 mol%), the reaction proceeded efficiently to give the expected 1,4-adduct (**3**) as the major product (entries 4—8). Especially, rhodium complexes with cod (cyclooctadiene) ligand worked effectively. Among them, $[RhCl(cod)]_2$ was found to be a suitable catalyst in terms of yield and selectivity of the products (**3**) (entry 8).

Next, the most suitable solvent for the reaction was investigated by use of $[RhCl(cod)]_2$ as the catalyst. When the reaction was attempted in aqueous ethereal solvents, the conjugate adduct (**3**) was produced in good yield, although the reaction required a prolonged time for completion (entries 8—10). A neutral protic solvent like ethanol was a good alternative to aqueous ethereal solvents (entry 11), while acetic acid was unsuitable because of decomposition of 1,5-azastibocine (**1a**). Aqueous dipolar solvents were appropriate for the reaction to give the conjugate adduct (**3**) in good yield in a short time (entries 12—14). Among them, aqueous NMP (*N*-methyl-2-pyrrolidinone) was found to be the best choice of solvent giving rise to the expected product (**3**) exclusively in 83% yield in 1 h and no Heck type adduct (**4**) was observed (entry 14). Water plays an important role in this reaction. When the reaction was conducted in dehydrated NMP, Heck type adduct (**4**) was formed in 9% yield which was never observed in aqueous NMP (entry 15).

Under this optimized condition, various *Sb*-aryl-1,5-azastibocines (**1a**—**d**) were reacted with methyl vinyl ketone (**2**) (Chart 1). Regardless of the electronic nature of the aryl group, all the 1,4-conjugate addition proceeded in 1 h at 100 °C in good yield. From these results, 1,5-azastibocines (**1**) were found to be good aryl donors in the 1,4-conjugate addition.

The reactions of *Sb*-phenyl-1,5-azastibocine (**1a**) with various enones and enoates were investigated (Table 2). The reactions with enone unsubstituted at β-position and with cyclic enones gave the expected 1,4-adducts in good yield (entries 1—3). However, the yields of the 1,4-adduct were decreased in the reaction of enones with bulky substituent at β-position (entry 4). In the reaction of enoates, steric hinderance of ester moiety did not affect the reaction because methyl, butyl, and *t*-butyl esters gave the corresponding 1,4-adducts in high yield (entries 5—7). However, substituent on double bond inhibited the 1,4-addition in moderate yield (entry 8).

Under the $[RhCl(cod)]_2$ catalyst in aqueous NMP, methyl vinyl ketone (**2**) also underwent 1,4-conjugate addition with triphenylstibane (Ph_3Sb) which was not activated by intramolecular N–Sb interaction. However, the reaction required a much longer time (24 h). The intramolecular N–Sb interaction in 1,5-azastibocine (**1**) contributed to activation of the aryl group on antimony and a reduction of the reaction time.

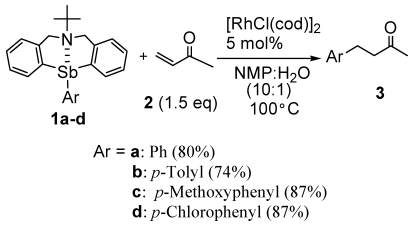
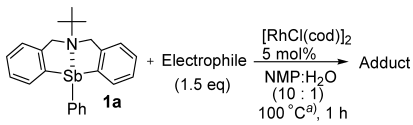
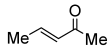
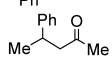
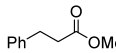
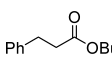
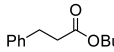
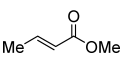
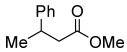


Chart 1. Reaction of Various *Sb*-Aryl-1,5-Azastibocines (**1**) with Methyl Vinyl Ketone (**2**)

A possible catalytic cycle for the conjugate addition was proposed which may be similar to the mechanism for the 1,4-addition of organoboronic acid to enones (Chart 2).[24—26] The aryl group on 1,5-azastibocine was transmetallated to rhodium catalyst to form aryl-rhodium complex (**A**). Insertion of α,β-unsaturated compound then took place to the aryl-rhodium bond to give η^3-oxa-π-allyl rhodium complex (**B**), which was hydrolyzed with water from aqueous solvent to give 1,4-conjugate adduct (**C**) and rhodium hydroxide (**D**). In the aqueous solvent, the hydrolysis process may be more favorable than the β-elimination process. So, no Heck-type

Table 2. Reaction of **1a** with Various Enones and Enoates



Entry	Electrophile	Conjugate adduct	Yield (%)[b]
1			80
2			80
3			92
4			59
5			84
6			94
7			99
8			66

a) Oil bath temperature. *b*) Isolated yield.

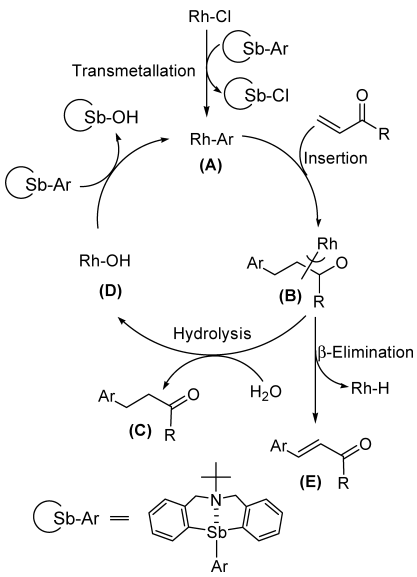


Chart 2. Possible Catalytic Cycle

adduct (**E**) was produced and almost exclusive formation of 1,4-conjugate adduct (**C**) was observed. The rhodium hydroxide (**D**) then underwent transmetallation by 1,5-azastibocine to regenerate aryl-rhodium complex (**A**).

Further application of **1** to various electron deficient olefins is under progress.

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