

Transition Metal Salts-Catalyzed Aza-Michael Reactions of Enones with Carbamates

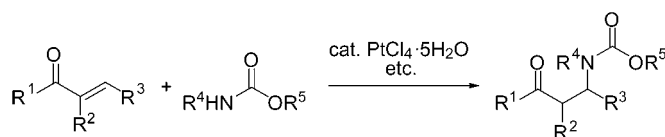
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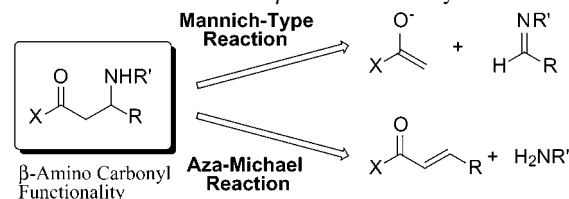
ABSTRACT



Several transition metal salts were found to catalyze aza-Michael reactions of enones with carbamates efficiently. The catalytic activity was strongly dependent on the nature of the metal salts. While conventional Lewis acids such as BF₃·OEt₂, AlCl₃, or TiCl₄ showed lower activity, group 7–11 transition metal salts in higher oxidation states such as ReCl₅, Fe(ClO₄)₃·9H₂O, RuCl₃·*n*H₂O, OsCl₃·3H₂O, RhCl₃·3H₂O, IrCl₄·*n*H₂O, PtCl₄·5H₂O, or AuCl₃·2H₂O exhibited higher catalytic activity.

The β-amino carbonyl functionality is not only a segment of biologically important natural products but also a versatile intermediate for the synthesis of nitrogen-containing compounds such as 1,3-amino alcohols, β-amino ketones, β-amino acids, and β-lactams.¹ Carbon–carbon bond formation between imines and enolates (Mannich-type reaction) is one of the powerful methods for the construction of this functionality,^{1d–h} and we have recently demonstrated that certain achiral² or chiral³ Lewis acids effectively catalyzed

Scheme 1. Construction of β-Amino Carbonyl Functionality



this type of reaction (Scheme 1). On the other hand, carbon–nitrogen bond formation between α,β-unsaturated carbonyl compounds and nitrogen nucleophiles (aza-Michael reaction) provides an alternative route to this functionality (Scheme 1).¹ⁱ

No catalyst is generally required in aza-Michael reactions with amines¹ⁱ or lithium amides⁴ as nucleophiles. Meanwhile, Lewis acidic metal catalysts have also been employed in less reactive aza-Michael reactions. A catalytic amount of FeCl₃, LiCl, HgCl₂,⁵ lanthanide triflates [Ln(OTf)₃, Ln = La, Sm,

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Yb],⁶ or InCl₃⁷ was reported to mediate the conjugate addition of aliphatic amines to α,β -unsaturated carbonyls in non-aqueous or aqueous solvents. Recently, Pd(II), Rh(I), Ir(I), and Ru(II) complexes have been reported to be effective for addition of amines to acrylic acid derivatives.⁸ With *O*-benzylhydroxyamine or aromatic amines as nucleophiles, asymmetric catalysis has been attained using chiral titanium, magnesium, and nickel compounds.^{9,10} An enantioselective aluminum catalyst has also been developed for the conjugate addition of hydrazoic acid to α,β -unsaturated imides.¹¹

While either a base or acid catalyst is used in aza-Michael reactions with a *less nucleophilic carbamate* (mostly intramolecular reactions),¹² Spencer et al. have quite recently demonstrated that PdCl₂(MeCN)₂ catalyzed intermolecular aza-Michael reactions of enones with benzyl carbamate as a nitrogen nucleophile.¹³ It is noted that such a less nucleophilic carbamate serves as a nitrogen nucleophile in the presence of the palladium catalyst to react intermolecularly with enones under mild conditions. In relation to our efforts to develop useful asymmetric synthetic methods for β -amino carbonyl compounds,^{2,3} we are interested in aza-Michael reactions of α,β -unsaturated carbonyls with carbamates. Herein, we report that several transition metal salts other than palladium salts are quite effective for the aza-Michael reactions of enones with carbamates.

First, we surveyed catalytic activity of various transition metal salts (mostly chlorides) in the reaction of phenyl propenyl ketone (**1a**) with benzyl carbamate (**2a**) in dichloromethane at room temperature (Table 1). Among the metal salts tested, ZrCl₄ (run 13), ReCl₅ (run 23), Fe(ClO₄)₃·9H₂O (run 24), RuCl₃·*n*H₂O (run 27), OsCl₃·3H₂O (run 28), RhCl₃·3H₂O (run 30), IrCl₄·*n*H₂O (run 32), PtCl₄·5H₂O (run 36), AuCl (run 39), and AuCl₃·2H₂O (run 40) were found to be effective as well as PdCl₂(MeCN)₂¹³ (run 34). On the other hand, lower yields were obtained with conventional oxophilic Lewis acids, i.e., BF₃·OEt₂, AlCl₃, SnCl₄, Sc(OTf)₃, and TiCl₄ (runs 1, 2, 5, 10, and 12). It is noteworthy that, unlike conventional Lewis acid-catalyzed reactions, group 7–11

Table 1. Catalytic Activity of Metal Salts

run	MX _n	time/h	yield/%
1	BF ₃ ·OEt ₂	2	20
2	AlCl ₃	6	trace
3	GaCl ₃	6	7
4	InCl ₃	6	NR ^a
5	Sc(OTf) ₃	2	8
6	YCl ₃ ·6H ₂ O	6	NR ^a
7	LaCl ₃ ·7H ₂ O	6	NR ^a
8	SbCl ₃	6	NR ^a
9	SiCl ₄	6	5
10	SnCl ₄	6	15
11	PbCl ₂	6	NR ^a
12	TiCl ₄	2	6
13	ZrCl ₄	6	70
14	HfCl ₄	6	53
15	VCl ₃	6	NR ^a
16	NbCl ₅	6	4
17	TaCl ₅	6	5
18	Cr(ClO ₄) ₃ ·6H ₂ O	6	31
19	MoCl ₃	6	trace
20	WCl ₅	6	9
21	Mn(ClO ₄) ₂ ·8H ₂ O	6	trace
22	ReCl ₃	6	12
23	ReCl ₅	6	96
24	Fe(ClO ₄) ₃ ·9H ₂ O	6	88
25	Fe(OTf) ₃	6	6
26	FeCl ₃	6	trace
27	RuCl ₃ · <i>n</i> H ₂ O	6	78
28	OsCl ₃ ·3H ₂ O	6	96
29	Co(ClO ₄) ₂ ·6H ₂ O	6	NR ^a
30	RhCl ₃ ·3H ₂ O	6	94
31	IrCl ₃ · <i>n</i> H ₂ O	6	12
32	IrCl ₄ · <i>n</i> H ₂ O	2	quant.
33	Ni(ClO ₄) ₂ ·6H ₂ O	6	trace
34	PdCl ₂ (CH ₃ CN) ₂	6	95
35	PtCl ₂	6	NR ^a
36	PtCl ₄ ·5H ₂ O	2	82
37	Cu(OTf) ₂	6	NR ^a
38	AgClO ₄	6	NR ^a
39	AuCl	6	quant.
40	AuCl ₃ ·2H ₂ O	2	91
41	Zn(ClO ₄) ₂ ·6H ₂ O	6	5
42	Cd(ClO ₄) ₂ ·6H ₂ O	6	11
43	HgCl ₂	6	NR ^a

^a No reaction occurred.

transition metals in the sixth period are effective in the present reaction and that metals in higher oxidation states, except for AuCl, showed higher catalytic activity.¹⁴

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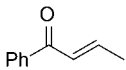
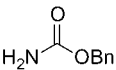
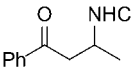
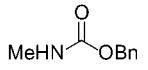
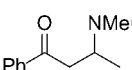
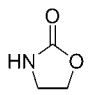
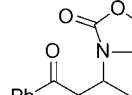
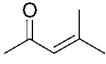
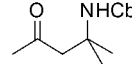
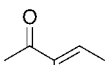
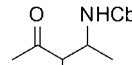
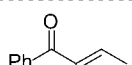
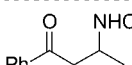
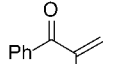
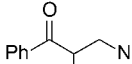
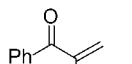
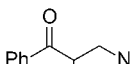

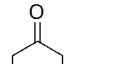
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Table 2. Aza-Michael Reactions of Various Enones **1** with Carbamates **2**^a

run	enones	nucleophiles	adducts	catalysts	time/h	yield/%
1	 1a	 2a	 3a	Fe(ClO ₄) ₃ ·9H ₂ O	6	88
				RhCl ₃ ·3H ₂ O	6	94
				IrCl ₄ ·nH ₂ O	2	quant.
				PtCl ₄ ·5H ₂ O	2	82
				AuCl ₃ ·2H ₂ O	2	quant.
				AuCl	6	91
				ReCl ₅	6	96
2	1a	 2b	 3b	PtCl ₄ ·5H ₂ O	24	quant.
3	1a	 2c	 3c	IrCl ₄ ·nH ₂ O	48	50
				PtCl ₄ ·5H ₂ O	48	96
				AuCl	48	54
				ReCl ₅	48	82
4	 1b	2a	 3d	PtCl ₄ ·5H ₂ O	24	59
				PtCl ₄ ·5H ₂ O	20	80 ^b
				AuCl ₃ ·2H ₂ O	20	51
				AuCl	20	65
5	 1c	2a	 3e	PtCl ₄ ·5H ₂ O	24	66
				PtCl ₄ ·5H ₂ O	20	75 ^b
				AuCl ₃ ·2H ₂ O	20	78
				AuCl	20	57
6	 1d	2a	 3f	PtCl ₄ ·5H ₂ O	20	65
				PtCl ₄ ·5H ₂ O	20	83 ^b
				PdCl ₂ (CH ₃ CN) ₂	20	11
7	 1e	2a	 3g	PtCl ₄ ·5H ₂ O	20	69
				PdCl ₂ (CH ₃ CN) ₂	20	9
8	 1f	2a	 3h	PtCl ₄ ·5H ₂ O	20	52
				PtCl ₄ ·5H ₂ O	20	68 ^b
				PdCl ₂ (CH ₃ CN) ₂	20	3
9	 1g	2a	 3i	PtCl ₄ ·5H ₂ O	24	42
				PtCl ₄ ·5H ₂ O	20	65 ^b

^a Enone:carbamate = 1.0:1.5, unless otherwise noted (see ref 15). ^b Enone:carbamate = 2.0:1.0.

We observed that most of the effective metal salts were partially soluble in dichloromethane and that the salts dissolved to some extent after adding the substrates. With an expectation to improve the catalytic activity, the use of acetonitrile and nitromethane as solvents, in which PtCl₄·5H₂O dissolves completely, was examined. Although PtCl₄·

5H₂O-catalyzed reactions of **1a** and **2a** in these solvents provided comparable yields of **3a** (85% and 89%, respectively) to that in dichloromethane (82%, Table 1, run 36), no significant improvement was observed. A less polar solvent, toluene, gave an inferior result (45%), while use of strongly coordinating solvents, DMSO, DMF, and THF, resulted in no reaction.

With several effective catalysts in hand, aza-Michael reactions of various enones with carbamates in dichloromethane at room temperature were next investigated (Table

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2).¹⁵ Benzyl *N*-methyl carbamate (**2b**) (run 2) and 2-oxazolidone (**2c**) (run 3) reacted smoothly with phenyl propenyl ketone (**1a**) to give the corresponding aza-Michael adducts **3b** and **3c** in high yields, while reactions of enones **1b–g** with benzyl carbamate (**2a**) provided adducts **3d–i** in moderate to high yields (runs 4–9). It is noteworthy that metal salts such as $\text{PtCl}_4 \cdot 5\text{H}_2\text{O}$ effectively catalyzed the reactions of α -substituted enones **1c–f** (runs 5–8) with **2a**, while the reactions proceeded sluggishly using $\text{PdCl}_2(\text{MeCN})_2$ as a catalyst.¹⁶ The reaction of an α,β -unsaturated ester such as methyl acrylate with **2a** was unproductive under these catalytic conditions as well as the palladium-catalyzed reaction.¹³

To get insight into the reaction mechanism, we performed several experiments as follows. First, the $\text{PtCl}_4 \cdot 5\text{H}_2\text{O}$ -catalyzed reaction of **1a** with **2a** was conducted in the presence of a radical inhibitor, 2,6-di-*tert*-butyl-4-methylphenol (BHT) or hydroquinone. The reactions proceeded smoothly to give **3a** in somewhat higher yields, 98% and 95%, respectively. Thus, the mechanism via the single electron transfer is unlikely in this reaction. Second, IR analysis of the acetonitrile solution of **2a** and $\text{PtCl}_4 \cdot 5\text{H}_2\text{O}$ (a 1:1 mixture) showed no significant change of the $\nu(\text{C}=\text{O})$ frequency of the carbamate (1735 cm^{-1} to 1734 cm^{-1}), while the acetonitrile solution of **2a** and $\text{Sc}(\text{OTf})_3$ exhibited a large shift of the frequency (1666 cm^{-1}). On the other hand, ^{13}C NMR analysis of a 1:1 mixture of $\text{PtCl}_4 \cdot 5\text{H}_2\text{O}$ and enone **1a** in CD_3CN showed almost no change in the chemical shifts of **1a**, while that of $\text{Sc}(\text{OTf})_3$ and **1a** exhibited large shift changes.¹⁷ It is suggested that the mode of interaction of the substrates with $\text{PtCl}_4 \cdot 5\text{H}_2\text{O}$ would differ from that of conventional oxophilic Lewis acids such as $\text{Sc}(\text{OTf})_3$. Third, when the isolated product **3d** was treated with a catalytic amount of $\text{PtCl}_4 \cdot 5\text{H}_2\text{O}$ (10 mol %) under the reaction conditions, the *retro*-aza-Michael reaction was

(15) **Experimental procedure:** To a metal salt (0.025 mmol, 0.1 equiv) in dichloromethane (1 mL) was added an enone (0.250 mmol, 1 equiv) and a carbamate (0.375 mmol, 1.5 equiv). After being stirred for 2–48 h at room temperature, the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 , filtered, and evaporated. The crude product was purified by preparative TLC to give a β -amino ketone.

(16) It was reported that the reaction of 3-methyl-3-penten-2-one (**1c**) with **2a** resulted in no reaction in the presence of $\text{PdCl}_2(\text{MeCN})_2$ as a catalyst; see ref 13.

(17) ^{13}C NMR (75 MHz, CD_3CN) **1a**: δ 191.1, 145.9, 138.9, 133.6, 129.6, 129.3, 128.3, 18.6. **1a**+ $\text{PtCl}_4 \cdot 5\text{H}_2\text{O}$ (a 1:1 mixture): δ 191.6, 146.6, 138.7, 133.8, 129.6, 129.3, 128.2, 18.6. **1a**+ $\text{Sc}(\text{OTf})_3$ (a 1:1 mixture): δ 198.1, 158.4, 137.1, 136.3, 131.8, 130.1, 127.8, 122.4, 19.9.

observed, i.e., benzyl carbamate (**2a**) was formed in 45% after 8 h. This result indicates that the reaction would be under thermodynamic control. Finally, the profiles of the reactions of **1a** with **2a** catalyzed by $\text{PtCl}_4 \cdot 5\text{H}_2\text{O}$ and $\text{PdCl}_2(\text{MeCN})_2$ at 10°C are shown in Figure 1. It turned out that

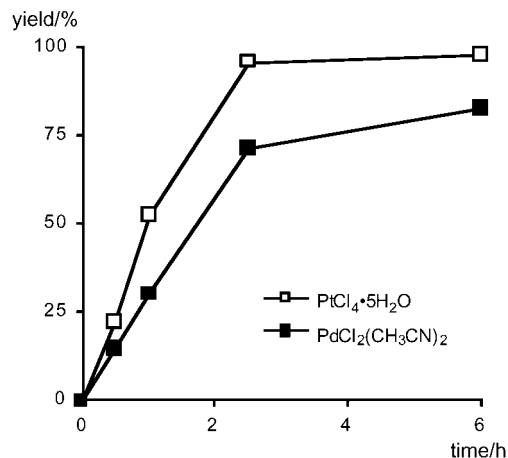


Figure 1. Plots of isolated yield of **3a** versus time for $\text{PtCl}_4 \cdot 5\text{H}_2\text{O}$ - and $\text{PdCl}_2(\text{MeCN})_2$ -catalyzed aza-Michael reactions of **1a** with **2a**.

the reaction with $\text{PtCl}_4 \cdot 5\text{H}_2\text{O}$ proceeded faster than that with $\text{PdCl}_2(\text{MeCN})_2$, giving >95% yield after 2.5 h. As already shown in Table 2, the differences in the catalytic activity between $\text{PtCl}_4 \cdot 5\text{H}_2\text{O}$ and $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ are remarkable when α -substituted enones are used (runs 5–8). It should be noted that this difference was observed even in the reaction of more reactive enone **1a**.

In summary, we have revealed that several transition metal catalysts, especially group 7–11 transition metal salts in higher oxidation states, were effective for aza-Michael reactions of enones with carbamates. Although the mechanism of the reaction is still unclear, asymmetric catalysis based on these metal salts might be possible. Further study along to this line is now in progress.

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