論文題目　Development of Catalytic C-N Bond Formation Reaction—Hydroamination of C-C Double Bonds and Direct Amination of Alcohols

(触媒的炭素—窒素結合形成反応の開発〜C-C二重結合のヒドロアミノ化とアルコールの直接的アミノ化)

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1. Heterobimetallic Catalysis in Asymmetric 1,4-Addition of O-Alkylhydroxylamine to α,β-Unsaturated N-Acylpyrrole

My first project was the development of a catalytic asymmetric *aza*-Michael reaction using rare earth metal-lithium-binaphthol (RELB) complexes. When I joined the group, my co-workers have established *aza*-Michael reaction using enones and RELB catalyst. Use of carboxylic acid derivatives was, however, difficult at that time. Therefore, I chose my theme as to broaden the substrate scope of the reaction to carboxylic acid derivatives. If the reaction scope was expanded, it leads to the synthesis of various useful chiral β-amino acid derivatives.

I planned my research strategy by considering following factors. 1) α,β-Unsaturated esters are unsuitable due to their high LUMO energy (poor reactivity). Activated carboxylic acid surrogates should be utilized. 2) Because RELB catalyst has suitable chiral environment towards enones that favor monodentate coordination mode, the use of monodentate carboxylic acid
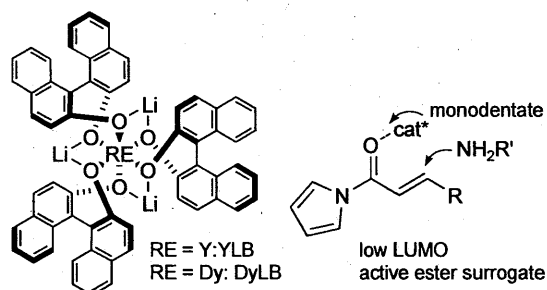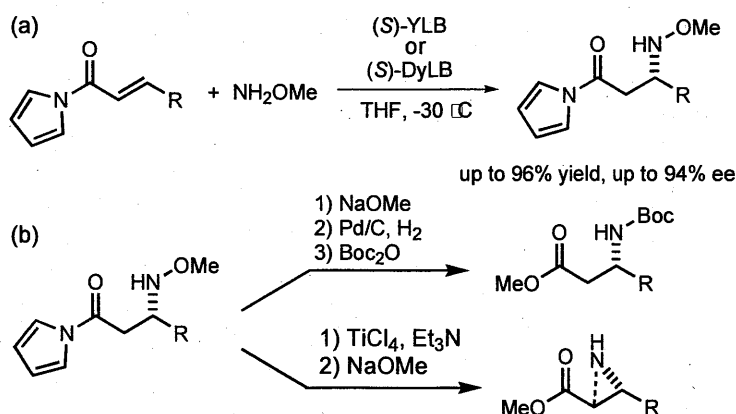

Figure 1. YLi₃tris[(S)-binaphthoxide](YLB), DyLi₃tris[(S)-binaphthoxide](DyLB), and α,β-unsaturated N-acylpyrrole.


Scheme 1. Catalytic asymmetric *aza*-Michael reaction and transformations.

surrogate is desirable. Therefore, I selected α,β-unsaturated N-acylpyrrole as a candidate. Due to aromaticity of pyrrole ring, the reactivity of N-acylpyrrole is supposed to be much higher than ester, amide and be as good as enones. Coordination mode of α,β-unsaturated N-acylpyrrole is also similar to enones. As expected, YLB (Y-Li-BINOL) and DyLB (Dy-Li-BINOL) (Figure 1) complexes pr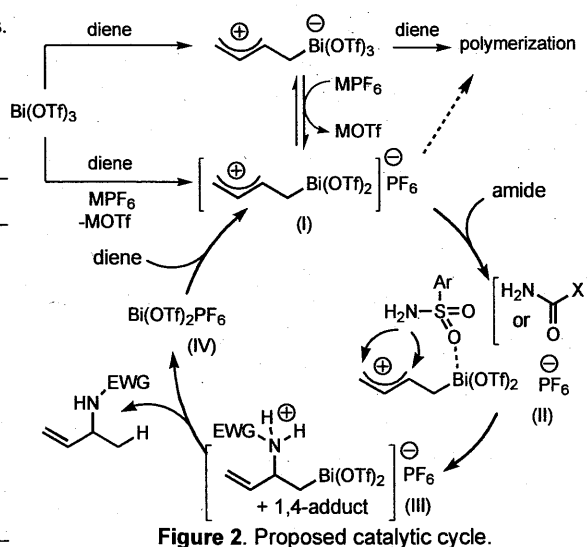omoted aza-Michael reactions of methoxylamine and α,β-unsaturated N-acylpyrroles, affording products in up to 96% yield and 94% ee (Scheme 1).[1] The product was successfully converted into β-amino esters and aziridines as shown in Scheme 1(b). I also established a new efficient method for the synthesis of various α,β-unsaturated N-acylpyrroles using HWE reaction.

2. Bismuth- and Hafnium-Catalyzed Intermolecular Hydroamination of 1,3-Dienes and Vinyl Arenes with Carbamates, Sulfonamides, and Carboxamides

Catalytic intermolecular hydroamination of olefins is an atom-economical method to provide nitrogen-containing building blocks. When I started this project, hydroamination of 1,3-diene investigated were limited to alkyl amines and aromatic amines. There was no report of intermolecular hydroamination reaction of 1,3-diene with weak nucleophiles like sulfonamides, carbamates, benzamides. Because 1,3-dienes readily polymerize, the key point of designing an efficient hydroamination of 1,3-dienes is how to suppress the polymerization, while promoting the desired 1:1 addition chemo-selectively. I planned to perform the reaction based on a new Lewis acid- π -acid dual controlling concept. If some metal complex can activate 1,3-dienes, and at the same time, locate amide close to the activated diene, the desired reaction would proceed faster than undesired polymerization (proximity-effect-control). After numerous investigations, combination of Bi(OTf)$_3$ and Cu(CH$_3$CN)$_4$PF$_6$ was found to be suitable, giving desired products in up to 96% yield (Table 1).[2] Detailed mechanistic studies showed that the exchange of PF$_6$ anion and ⁻OTf anion gave more cationic Bi(OTf)$_2$PF$_6$ species which plays a significant role in the proposed catalytic cycle in Figure 2. Bi(OTf)$_2$PF$_6$ not only activates 1,3-dienes to generate cationic species, but also interacts with amides to fix amides in close proximity.

Table 1. Catalytic hydroamination of 1,3-diene with amides.

entry	nucleophile		temp (℃)	time (h)	yield (%)
1		R = CH$_2$Ph	50	18	80
2		R = CH$_3$	50	18	96
3	H$_2$N—C(O)—OR	R = n-Bu	50	18	85
4			50	18	92
5		R = Ph	50	3	80
6		R = p-tol	50	3	84
7	H$_2$N—S(O)$_2$—R	R = p-MeO-C$_6$H$_4$	50	5	84
8		R = p-CF$_3$-C$_6$H$_4$	50	5	75
9		R = o-NO$_2$-C$_6$H$_4$	25	24	67
10	H$_2$N—C(O)—R	R = Ph	100	12	75
11		R = p-CF$_3$-C$_6$H$_4$	90	17	77

Figure 2. Proposed catalytic cycle.

Considering the allylic bismuth species (□) in Figure 2, the reaction with vinyl arenes can also form similar bismuth

species. Therefore, I speculated that the bismuth catalyst would catalyze the hydroamination of vinyl arenes. When 2-oxazolidone was used, however, yield was poor using the bismuth catalyst. Further metal screening revealed that $Hf(OTf)_4$ was more reactive than $Bi(OTf)_3$. $Hf(OTf)_4/Cu(CH_3CN)_4PF_6$ system promoted the reaction with 2-oxazolidone nicely in good yield. The $Hf(OTf)_4/Cu(CH_3CN)_4PF_6$ system was applicable to the hydroamination of wide range of vinyl arenes, including less reactive vinyl arenes with electron-withdrawing groups and a readily polymerizable vinyl arene with an electron-donating group. In case of a vinyl arene with an electron-donating group, reaction was performed at 8 °C to avoid self-polymerization.
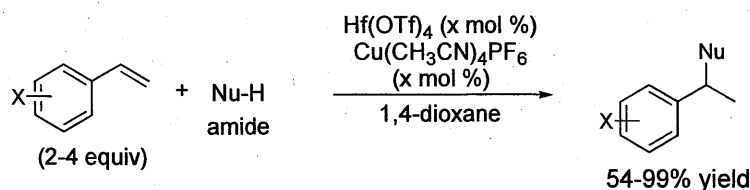
Scheme 2. Hafnium catalyzed hydroamination of styrene.

3. Bismuth-Catalyzed Direct Substitution of the Hydroxyl Group in Alcohols with Sulfonamides, Carbamates, and Carboxamides
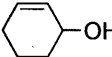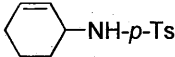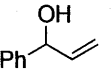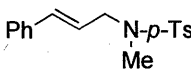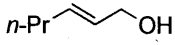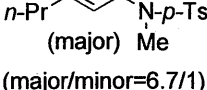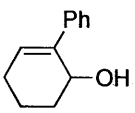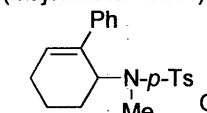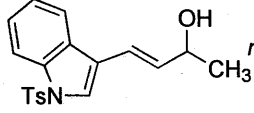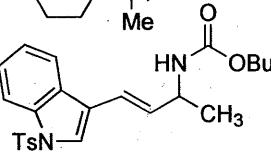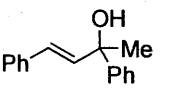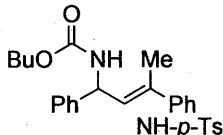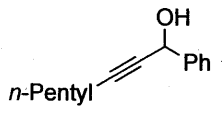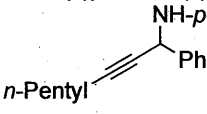
Substitution of the hydroxyl group in alcohols by amine nucleophiles generally requires pre-activation of the alcohols because of the poor leaving ability of the hydroxyl group. Alcohols are generally transformed into corresponding halides, carboxylates, or related compounds with good leaving ability. The process inevitably produces stoichiometric amounts of salt-waste. Substitution of the halides and related compounds also produces salt-waste and requires stoichiometric amounts of base. Therefore, direct catalytic substitution of alcohols with amines is desirable. In part 2, the $Bi(OTf)_3/MPF_6$ (M = K or Cu) system not only activates 1,3-dienes as π-acid, but also controls the position of amide nucleophiles as a Lewis acid. I hypothesized that bismuth catalysis would also be suitable for activation of allylic and propargylic alcohols.

With the $Bi(OTf)_3/MPF_6$ (M = K or Cu) system, various allyl alcohols and propargyl alcohols were efficiently transformed into corresponding allylic and propargylic amides in 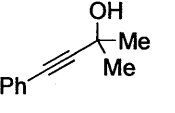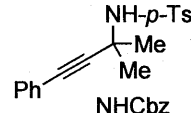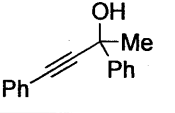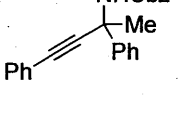good yield (Table 2).[4] Mechanistic studies showed that even with co-existence of base like K_2CO_3, the reaction proceeded without any problem to give desired product at similar efficiency. When using chiral allyl and propargyl alcohols, racemic allylic amides were obtained, implying the formation of carbenium intermediate.

References:

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2. Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611.

3. Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 150.

4. Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.

Table 2. Direct catalytic allylic and propargylic substitution of various alcohols with amides.

$$\text{alcohol} + \text{Nu-H} \xrightarrow[\substack{\text{dioxane, rt} \\ \text{Drierite (CaSO}_4\text{)}}]{\substack{\text{Bi(OTf)}_3 \text{ (5 mol \%)} \\ \text{KPF}_6 \text{ (5 mol \%)}}} R^1 \diagdown\diagup \overset{\text{Nu}}{\underset{R^2}{\overset{|}{C}}} R^3$$

entry	alcohol	Nu-H (equiv)	product	time (h)	% yield
1	cyclohexenyl-OH	p-TsNH₂ (2)	cyclohexenyl-NH-p-Ts	2	96
2	Ph, OH, allyl	p-TsNHMe (3)	Ph⌒⌒N-p-Ts, Me	17	62
3[a]	n-Pr⌒⌒OH	p-TsNHMe (3)	n-Pr⌒⌒N-p-Ts (major) Me (major/minor=6.7/1)	7	63
4	Ph, cyclohexenyl-OH	p-TsNHMe (3)	Ph, cyclohexenyl-N-p-Ts, Me	17	74
5	indolyl⌒⌒, OH, CH₃, TsN	n-BuOCONH₂ (1)	indolyl⌒⌒, HN-C(O)OBu, CH₃, TsN	0.2	84
6	Ph⌒, OH, Me, Ph	n-BuOCONH₂ (1.5)	BuO-C(O)-NH, Me, Ph, Ph	0.1	60
7	n-Pentyl≡, OH, Ph	p-TsNH₂ (1.5)	n-Pentyl≡, NH-p-Ts, Ph	8	78
8	Ph≡, OH, Me, Me	p-TsNH₂ (2)	Ph≡, NH-p-Ts, Me, Me	4	63
9	Ph≡, OH, Me, Ph	NH₂Cbz (2)	Ph≡, NHCbz, Me, Ph	5	65

[a] Reaction was run at 40 °C.

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