論文の内容の要旨

論文題目

Development of Cp*Co^{III}-Catalyzed C-H Bond Addition Reactions to Electrophiles
(Cp*Co^{III} 触媒による C-H 結合の求電子剤への付加反応の開発)

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Research background

Nucleophilic addition of organometallic reagents to polar electrophiles, such as aldehydes, imines and Michael acceptors, is a fundamental C-C bond-forming reaction in organic synthesis. Generation of carbon nucleophiles, however, generally requires stoichiometric amounts of strong bases or reducing metals, which inevitably produces salt wastes. Moreover, functional group compatibility is often problematic due to strong basicity and reactivity of thus-generated nucleophiles. Recently, Cp*Rh^{III} catalysts (Cp* = pentamethylcyclopentadienyl) were reported to catalyze the addition of directed aromatic C-H bonds to imines[1] and other electrophiles[2]. Although these catalytic processes are quite atom economical and functional group compatible, the need for expensive and precious rhodium sources is economically and environmentally disadvantageous. Herein, development of more accessible cobalt catalyst for C-H bond activation and addition reactions to electrophiles is described.

Addition of 2-phenylpyridine to imines

The reported rhodium catalysis[1] prompted me to employ cationic Co^{III} catalysts with 3 or more free coordination sites. Therefore, I started the investigation by synthesizing several cationic cyclopentadienylcobalt complexes with a dissociable benzene ligand[3] and evaluating their catalytic activity in addition reaction of 2-phenylpyridine **1a** to sulfonylimine **2a** (Table 1). Cp*Co^{III} complex **4a** showed the highest efficiency and **3aa** was obtained in 80% yield. While bulkier substituents decreased reactivity (**4b**, **4d**, **4e**), less sterically hindered catalyst **4c** also afforded lower yield probably due to the instability of the catalyst.

The scope of imines is summarized in Table 2. Satisfactory yield was obtained with various kinds of aromatic and heteroaromatic imines (entries 1-11). α,β-Unsaturated imine **2l**, however, afforded complex mixture owing to the competing conjugated addition reaction (entry 12). Aliphatic imine **2m** was also not applicable and isomerization to the enamide was faster than the desired reaction (entry 13).

Table 1. Catalyst screening

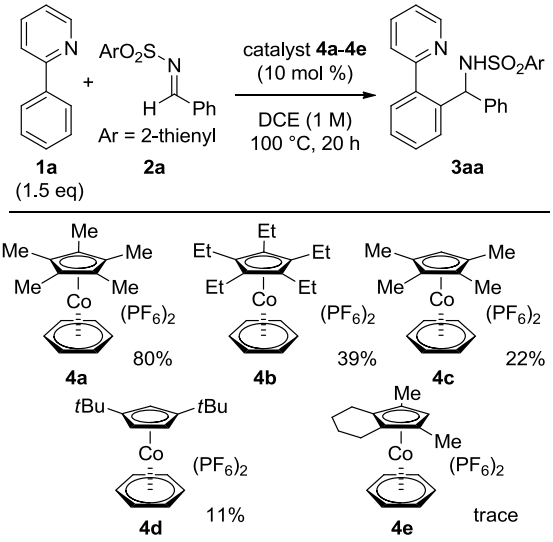
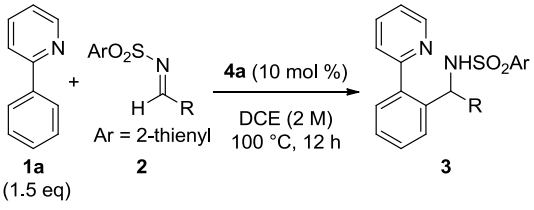


Table 2. Addition of 2-phenylpyridine to various imines



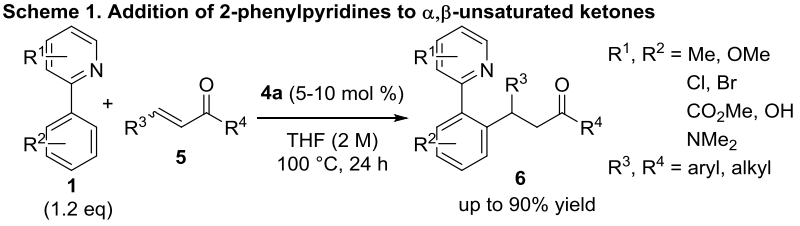
Entry	R : Imine **2**		Product	Yield (%)
1	Ph	**2a**	**3aa**	80
2	2-naphthyl	**2b**	**3ab**	79
3	*p*ClC$_6$H$_4$-	**2c**	**3ac**	83
4	*p*BrC$_6$H$_4$-	**2d**	**3ad**	72
5	*p*CF$_3$C$_6$H$_4$-	**2e**	**3ae**	64
6	*m*ClC$_6$H$_4$-	**2f**	**3af**	76
7	*p*MeC$_6$H$_4$-	**2g**	**3ag**	76
8	*p*MeOC$_6$H$_4$-	**2h**	**3ah**	57
9	*o*MeC$_6$H$_4$-	**2i**	**3ai**	71
10	2-thienyl	**2j**	**3aj**	69
11	2-furyl	**2k**	**3ak**	66
12	(*E*)-cinnamyl	**2l**	**3al**	messy
13	cyclohexyl[a]	**2m**	**3am**	<30

a) Ar = *p*MeC$_6$H$_4$-

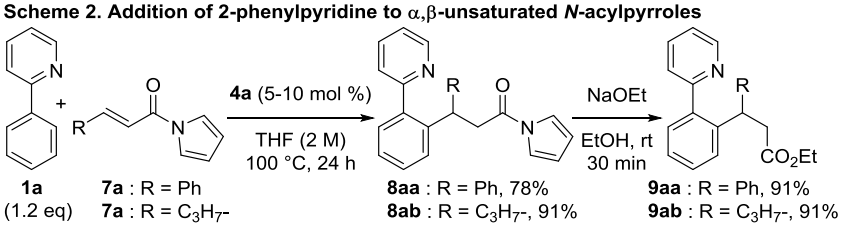
Addition to Michael acceptors

The same catalyst **4a** also catalyzed the conjugated addition reaction to enones **5** (Scheme 1). Although neither enals nor α,β-unsaturated esters could be utilized as electrophiles, α,β-unsaturated *N*-acylpyrroles **7** afforded the desired products **8** in good yield (Scheme 2). The products **8** were readily converted to corresponding esters **9** with NaOEt.

Scheme 1. Addition of 2-phenylpyridines to α,β-unsaturated ketones



Scheme 2. Addition of 2-phenylpyridine to α,β-unsaturated *N*-acylpyrroles



Reaction mechanism

A plausible reaction mechanism based on the rhodium catalysis[1c,d] is described in Figure 1. Initially, the coordinating benzene of **4a** would dissociate upon heating, and 2-phenylpyridine complex **I** would be generated. The process of C-H activation is assumed to proceed via electrophilic aromatic substitution or concerted metalation deprotonation mechanism to form cyclometalated intermediate **II**. After ligand exchange (**III**) and insertion of electrophiles (**IV**), proto-demetalation from **V** with another 2-phenylpyridine (or with acidic proton captured at the step from **I** to **II**) would dissociate the products

and regenerate the key intermediate **II**.

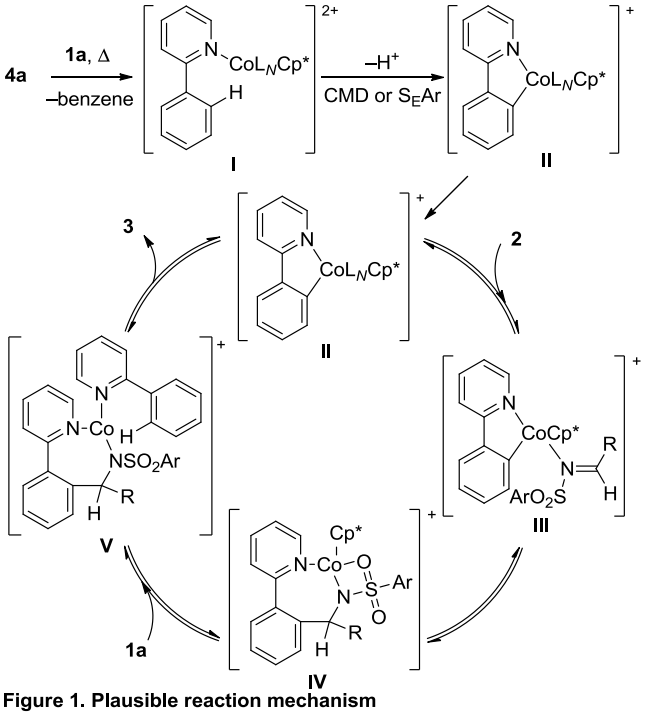


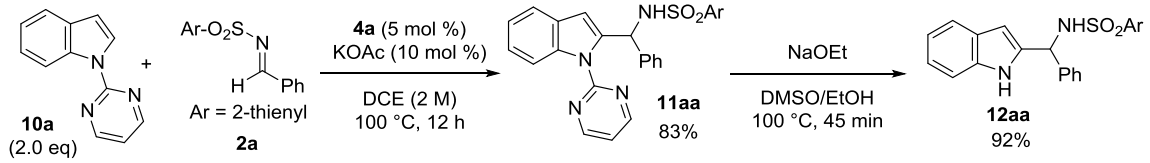
Figure 1. Plausible reaction mechanism

C2-Selective addition of indoles to imines

With the optimal catalyst in hand, I turned my attention into C2-selective functionalization of indoles with electrophiles. Indole is an electron-rich heteroaromatic ring and it can react with electrophiles selectively at its C3-position. In contrast, C2-selective functionalization requires reduction of indoles to dihydroindoles[4] or directed metalation by stoichiometric amounts of strong bases, such as BuLi. Hence, more functional group compatible and atom-economical methods are desirable. Because C2-selective metalation of indoles with directing groups on their nitrogen atom in transition metal-catalyzed reactions has been well studied[5], C2-selective reaction with electrophiles under the Cp*Co^{III} catalysis was expected to proceed. During my investigation, Cp*Rh^{III}-catalyzed C2-selective addition of carbamoyl-protected indoles to imines was reported[6]. However, there still remains room for improvement in terms of the relatively high catalyst loading of the precious rhodium catalyst and moderate turnover number.

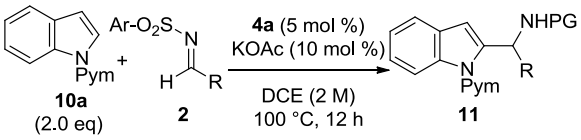
After optimization of the reaction conditions, addition of 2-pyrimidyl-protected indole **10a** to imine **2a** proceeded and **11aa** was obtained in 83% yield with complete regioselectivity (Scheme 3). Selection of a directing group of indole was the most important. 2-Pyrimidyl group was selected due to the high reactivity and removability. Addition of KOAc effectively suppressed formation of unidentified byproducts. Removal of the 2-pyrimidyl group was accomplished by heating with NaOEt to afford **12aa**.

Scheme 3. Optimized conditions for C2-selective addition of indoles to imines



The substrate scope is shown in Table 3 and Scheme 4. In addition to aromatic and heteroaromatic imines (Table 3 entries 1-12, 15), aliphatic imine **2m** was also applicable (entry 14). No isomerization to the enamide was observed. The catalyst loading was successfully decreased to 0.5 mol % to achieve high TON, around 180 (entry 16). Various substituted indoles also afforded the product in moderate to good yield (Scheme 4, **11bc**-**11ic**).

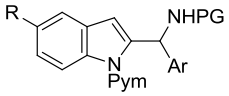
Table 3. Addition of indole to imines: scope of imines



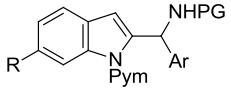
Entry	R	Ar	Imine	Product	Yield (%)
1	Ph	2-thienyl	**2a**	**11aa**	83
2	2-naphthyl	2-thienyl	**2b**	**11ab**	78
3	*p*ClC$_6$H$_4$-	2-thienyl	**2c**	**11ac**	89
4	*p*BrC$_6$H$_4$-	2-thienyl	**2d**	**11ad**	91
5	*p*CF$_3$C$_6$H$_4$-	2-thienyl	**2e**	**11ae**	93
6	*p*CO$_2$MeC$_6$H$_4$-	2-thienyl	**2n**	**11an**	90
7	*m*ClC$_6$H$_4$-	2-thienyl	**2f**	**11af**	90
8	*p*MeC$_6$H$_4$-	2-thienyl	**2g**	**11ag**	71
9	*p*MeOC$_6$H$_4$-	2-thienyl	**2h**	**11ah**	48
10	*o*MeC$_6$H$_4$-	2-thienyl	**2i**	**11ai**	74
11	2-thienyl	2-thienyl	**2j**	**11aj**	58
12	2-furyl	2-thienyl	**2k**	**11ak**	64
13	(*E*)-cinnamyl	2-thienyl	**2l**	**11al**	38
14	cyclohexyl	*p*MeC$_6$H$_4$-	**2m**	**11am**	87
15	Ph	*p*MeC$_6$H$_4$-	**2o**	**11ao**	78
16[a]	*p*ClC$_6$H$_4$-	2-thienyl	**2c**	**11ac**	91

a) 0.5 mol % of **4a** and 1.0 mol % of KOAc were used.

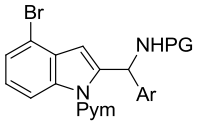
Scheme 4. Addition of indoles to imine: scope of indoles



R = Me, **11bc**, 89%
R = OMe, **11cc**, 84%
R = Cl, **11dc**, 88%
R = Br, **11ec**, 87%
R = CO_2Me, **11fc**, 77% (120 °C)



R = Me, **11gc**, 89%
R = OBn, **11hc**, 62%



11ic, 88%

Summary

Cationic Cp*Co^{III} catalyst **4a** effectively catalyzed the addition of aromatic C-H bonds to electrophiles in the presence of the appropriate directing group[7]. C2-selective functionalization of indoles was also achieved with higher efficiency compared with reported Cp*Rh^{III} catalysis[8]. Further application to synthetically useful transformations and investigation of the unique reactivity of the cobalt catalyst are in progress.

References

(1) a) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1248; b) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2115; c) Tauchert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 1482; d) Li, Y.; Zhang, X.-S.; Li, H.; Wang, W.-H.; Chen, K.; Li, B.-J.; Shi, Z.-J. *Chem. Sci.* **2012**, *3*, 1634. (2) a) Yang, L.; Correia, C. A.; Li, C.-J. *Adv. Synth. Catal.* **2011**, *353*, 1269; b) Yang, L.; Correia, C. A.; Li, C.-J. *Org. Biomol. Chem.* **2011**, *9*, 7176; c) Yang, L.; Qian, B.; Huang, H. *Chem.Eur. J.* **2012**, *18*, 9511. (3) Kölle, U.; Fuss, B.; Rajasekharan, M. V.; Ramakrishna, B. L.; Ammeter, J. H.; Böhm, M. C. *J. Am. Chem. Soc.* **1984**, *106*, 4152. (4) H. Çavdar, N. Saraçoglu, *Tetrahedron* **2005**, *61*, 2401. (5) a) Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910; b) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4698. (6) Zhou, B.; Yang, Y.; Lin, S.; Li, Y. *Adv. Synth. Catal.* **2013**, *355*, 360. (7) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2207. (8) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Chem. Eur. J.* **2013**, *19*, 9142.