論文の内容の要旨

Investigation into New Catalytic Systems for Cross-Dehydrogenative Coupling Reactions under Aerobic Conditions

（酸素雰囲気下における脱水素クロスカップリング反応のための新規触媒系の研究）

田上　新

Introduction

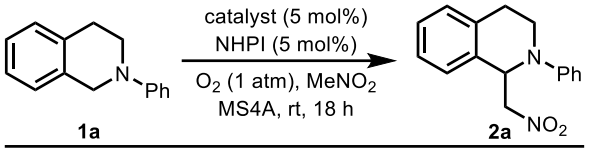
Over the past hundred years, significant progress in organic chemistry has been made. However, regio-selective C-H functionalization still remains a challenging topic. Recently, cross-dehydrogenative coupling (CDC) reactions of amines or ethers have emerged as a novel method in which α-selective C-H functionalization is achievable. Thus far, several transition metals have been reported as catalysts for CDC reactions. As for the metal-free reactions, some methods have been developed but examples are still rare. In addition, these oxidative coupling reactions often required stoichiometric amounts of oxidants such as *t*-BuOOH, DDQ, and so on. Thus, the use of molecular oxygen as an oxidant is more beneficial for the environment and a desired goal. Based on these facts, I decided to explore novel metal-free CDC reactions of amines under aerobic conditions. During the course of my investigation, I discovered antimony and sulfuryl chloride as novel catalysts for transition metal-free and metal-free reactions, respectively.

1. Antimonate/NHPI-Catalyzed CDC Reaction of Tertiary Amines

In order to achieve a metal-free CDC reaction, I hypothesized that aminium radical cation could serve as a catalyst. Aminium radicals are known as single electron oxidants, whose oxidation potentials are tunable by modifying the substituents on aromatic moiety. Since substoichiometric use of these species for an oxidation reaction was recently reported, there was the possibility to catalyze CDC reactions. In addition, I hypothesized that *N*-hydroxyphthalimide (NHPI), which is effective for hydrogen radical abstraction, would promote the reaction. Thus, I initially attempted the nitromethylation reaction of *N*-

phenyltetrahydroisoquinoline (**1a**) under oxygen atmosphere using tris(*p*-bromophenyl)aminium hexachloro-antimonate and NHPI as catalysts (Table 1, entry 1). Although antimony is classified as a semi-metal, I speculated that counter anion could be replaced at a latter stage. To our delight, nitromethylated product (**2a**) was furnished in a good yield. In order to survey the effect of counter anions, hexafluoroantimonate salt was prepared and tested, which also provided the product in a modest yield (entry 2). However, when tetra-fluoroborate or hexafluorophosphate salts were utilized, the reactions were very sluggish (entries 3-4). Instead, when the counter cation was replaced with tetraethylammonium or trityl cations, **2a** was obtained in modest yields (entries 5-6). Based on these experiments, I concluded that antimonate anion served as a catalyst for the oxidative coupling reaction. The use of antimony in the oxidative coupling reaction seemed interesting since: (i) antimony is semi-metal and inexpensive; (ii) the use of antimony in CDC reaction of amines has not been reported; and (iii) hexahaloantimonate anions have been generally considered as stable and innocent counter anions in organic chemistry. Thus, I decided to further investigate antimonate as a catalyst. Since nitromethylation was also catalyzed by antimony pentachloride, I determined that antimony was the real active species (entry 7). After examining various sources of antimony, sodium hexachloroantimonate turned out to be the best catalyst (entry 8).

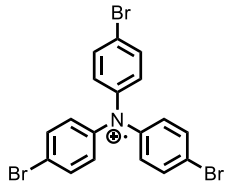
Table 1. Investigation of active species



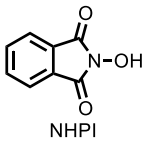
1a **2a**

Entry	Catalyst	Yield (%)[a]
1	Ar_3NSbCl_6	64
2	Ar_3NSbF_6	41
3	Ar_3NBF_4	6
4	Ar_3NPF_6	11
5	Et_4NSbCl_6	51
6	Ph_3CSbCl_6	41
7	$SbCl_5$	53
8	$NaSbCl_6$(α-$NaphNO_2$)	>95

[a] Determined by ^{1}H NMR analysis.



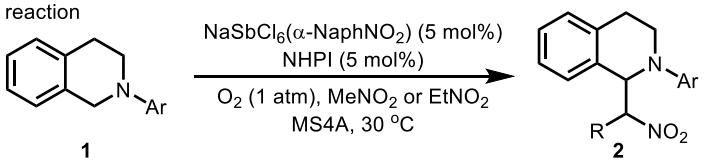
aminium radical (Ar_3N)



NHPI

After optimization of the reaction conditions, the substrate generality of this oxidative coupling reaction was investigated (Table 2). In addition to *N*-phenyl-substituted tetrahydroisoquinolines, substrates which possess electron-rich aromatic groups furnished the products in high yields (entries 1-5). On the other hand, an electron-deficient amine was less reactive (entry 6). In addition to nitromethane, nitroethane was also shown to react smoothly despite with modest regio-selectivity (entry 7). In addition to nitroalkanes, various nucleophiles were applicable under similar reaction conditions.

Table 2. Substrate scope of Sb/NHPI-catalyzed CDC reaction



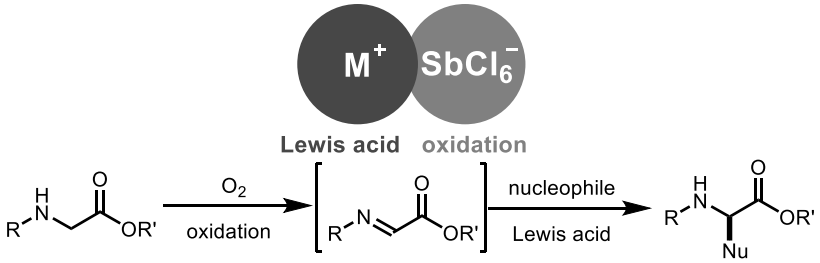
1 **2**

Entry	Ar	Nucleophile	Time (h)	Yield (%)[a]
1	Ph	$MeNO_2$	4	90 (85)
2	4-MeO-C_6H_4	$MeNO_2$	5	>95 (82)
3	3-MeO-C_6H_4	$MeNO_2$	39	73 (74)
4	2-MeO-C_6H_4	$MeNO_2$	48	89 (86)
5	4-Me-C_6H_4	$MeNO_2$	13	87 (83)
6	4-Cl-C_6H_4	$MeNO_2$	11	57 (53)
7[b]	Ph	$EtNO_2$	24	73 (64)

[a] Determined by ^{1}H NMR analysis. Isolated yield is shown in parentheses.
[b] Dr = 1.6 : 1.

2. Zinc Antimonate-Catalyzed Oxidative Allylation of α-Amino Acid Derivatives

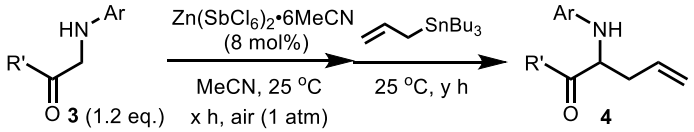
Scheme 1. Concept of bifunctional catalyst



Although antimony-catalyzed CDC reaction of tertiary amines was attractive, viable substrates were limited only to *N*-aryltetrahydroisoquinolines. In order to solve this problem, I hypothesized that *N*-aryl-substituted glycine derivatives would be alternative candidates since higher acidity of α-hydrogen of α-amino acid derivatives may facilitate oxidation process. In addition to this hypothesis, I developed a novel concept of employing metal antimonate as a new class of bifunctional catalyst, where the metal cation serves as a Lewis acid to promote nucleophilic addition and the antimonate anion serves as a catalyst for aerobic oxidation. Based on these hypotheses, I initially attempted the CDC reactions using protic nucleophiles such as nitromethane. However, none of these nucleophiles furnished desired products in acceptable yields. Instead, it turned out that allyltributyltin was a stable and reactive nucleophile. Among several metal Lewis acids I examined, zinc(II) was found to be the best Lewis acid. Thus, zinc hexachloroantimonate was prepared and employed as a bifunctional catalyst. Although zinc antimonate served as a bifunctional catalyst for the oxidative allylation reaction of glycine derivatives, several disadvantages limited the synthetic utility of this catalyst. For example, since oxidation was inhibited in the presence of allyltin, allyltin was added after completion of oxidation reaction. In addition, it was found that not only zinc, but also antimony species seemed to serve as a Lewis acid. Finally, due to competing side-reactions, yields were relatively moderate.

After optimization of reaction conditions, the substrate scope of this oxidative allylation reaction was investigated (Table 3). In addition to a glycine ethyl ester, which has *p*-methoxyphenyl (PMP) group on the nitrogen, methyl, isopropyl, benzyl esters provided the allylated products in good yields (entries 1, 3, 5), while sterically hindered *t*-butyl ester was less reactive (entry 4). As for glycine amides, the methyl amide gave the corresponding product in a high yield (entry 6), while ethyl and benzyl amides afforded products in

Table 3. Substrate scope of zinc antimonate-catalyzed oxidative allylation



Entry	R	Ar	Time (h)	Yield (%)[a]
1	MeO	PMP	2+2	63 (60)
2	EtO	PMP	2+2	75 (71)
3	*i*-PrO	PMP	2+2	63 (55)
4	*t*-BuO	PMP	2+2	39 (34)
5	BnO	PMP	2+2	64 (58)
6	MeNH	PMP	2+2	76 (71)
7	EtNH	PMP	2+2	37
8	BnNH	PMP	2+2	38
9	$(CH_2)_4N$	PMP	2+2	56 (54)
10	EtO	2,6-Me_2-4-MeO-C_6H_4	2+2	63 (53)
11	EtO	2,6-Br_2-4-MeO-C_6H_4	18	no oxidation
12[b]	EtO	4-Me-C_6H_4	5+3	30
13[b]	EtO	Ph	1+2	28
14	MeO_2CCH_2NH	PMP	2+2	56 (55)

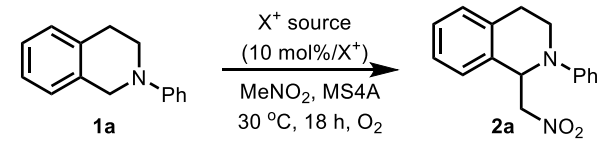
[a] Determined by ^{1}H NMR analysis. Isolated yield is shown in parentheses.
[b] 7.5 mol% catalyst was used.

modest yields (entries 7, 8). Pyrrolidine-substituted amide was also found to be reactive (entry 9). When the aryl group on the nitrogen was modified, 2,6-dimethyl-4-methoxyphenyl substrate reacted smoothly (entry 10). On the other hand, no oxidation took place for the 2,6-dibromo-4-methoxyphenyl substrate (entry 11). Compared with the PMP substrate, *p*-tolyl and phenyl substrates were less reactive (entries 12, 13). Finally, when a peptide was subjected to the same reaction conditions, the α-hydrogen of the glycine which possess PMP group on it was selectively functionalized (entry 14).

3. Sulfuryl Chloride-mediated CDC reaction of Tertiary *N*-Aryl Amines

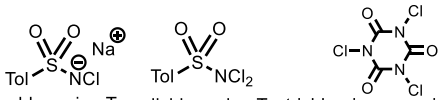
During the course of my investigation into the antimony-catalyzed oxidative coupling reactions, it was found that *N*-chlorosuccinimide (NCS) can serve as a catalyst for the CDC reaction of *N*-phenyltetrahydroisoquinoline (Table 4, entry 1). When other electrophilic chlorine sources were examined, most catalysts provided the desired product in low yields (entries 2-5). On the other hand, sulfuryl chloride turned out to be the most effective catalyst (entry 6). Further optimization revealed that the use of 6 mol% sulfuryl chloride afforded the product in an excellent yield (entry 7). In contrast, reactions with other electrophilic halogen sources such as *N*-bromosuccinimide (NBS) and iodine were very sluggish (entries 8, 9). The reactions are believed to proceed through a radical-initiated autoxidation mechanism.

Table 4. Metal-free CDC reaction



Entry	X^+ source	Yield (%)[a]	
		2a	rec. **1a**
1	NCS	60	32
2	^{t}BuOCl	10	91
3	chloramine T	8	95
4	dichloramine T	4	95
5	trichloroisocyanuric acid	4	99
6	SO_2Cl_2	75	trace
7[b]	SO_2Cl_2	93	ND
8	NBS	3	95
9	I_2	15	85

[a] Determined by ^{1}H NMR analysis. [b] 6 mol% catalyst was used.



Conclusion

Antimony was found to be a novel catalyst for the cross-dehydrogenative coupling reactions of tertiary amines under mild aerobic conditions in the presence of NHPI as a co-catalyst. Based on this initial discovery, a novel bifunctional catalyst was developed for the α-functionalization of more synthetically useful glycine derivatives. Although antimony is classified as a semi-metal, the use of antimony for CDC reactions is novel since hexachloroantimonate anion has long been recognized as a stable and innocent counter anion in the field of organic chemistry. The present work dispels this widely regarded assumption. Finally, the metal-free CDC reaction was achieved by using sulfuryl chloride as a non-metal catalyst.