論文の内容の要旨

Soft Lewis Acid/Hard Brønsted Base Cooperative Catalysis in Direct Asymmetric C–C Bond-Forming Reactions

（ソフト Lewis 酸/ハード Brønsted 塩基協奏触媒を用いた
直接的不斉炭素—炭素結合形成反応 ）

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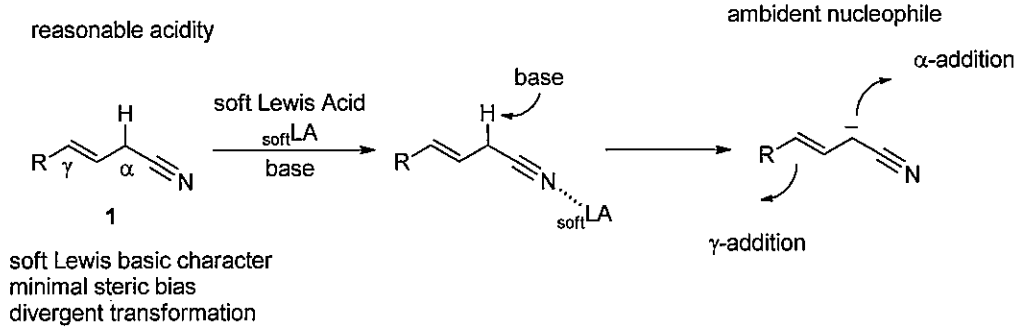
1. Direct Catalytic Asymmetric Addition of Allylic Cyanides to Ketoimines

Construction of stereogenic center through catalyst-controlled asymmetric C–C bond formation is regarded as the most efficient methodology for the synthesis of optically active compounds. In particular, the "direct reactions" which proceed under proton transfer conditions without preactivation of pronucleophile are desirable in terms of atom and step economy. However, in situ catalytic generation of active carbon nucleophiles coupled with subsequent asymmetric intermolecular C–C bond formation via proton transfer remains a formidable task in modern organic chemistry, especially for the catalytic asymmetric access to tetrasubstituted stereogenic center. Asymmetric additions of carbon nucleophiles to simple ketones and ketoimines are most efficient and straightforward approach to this important class of compounds bearing oxygen or nitrogen functionality. In contrast to a number of reported examples of asymmetric additions to aldehydes and aldimines, relatively few exist for ketones and ketoimines counterpart because of their attenuated reactivity and lesser steric dissimilarity of the substituents at the prochiral sp^2 carbons.

Scheme 1. Allylic Cyanide as Ambident Nucleophile

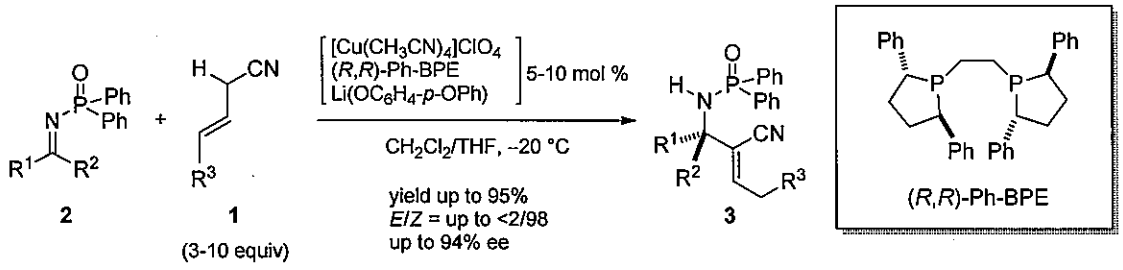


In this context, I envisioned to use allylic cyanides **1** as potential pronucleophiles for the asymmetric addition to ketones and ketoimines because (1) the minimal steric bias of the nitrile

group is beneficial for the highly congested transition state anticipated for the reaction with ketones and ketoimines; (2) the soft Lewis basic character of the nitrile functionality allows for chemoselective activation in the presence of a soft Lewis acid; (3) the adjacent vinyl group enhances the acidity of the α-hydrogen of the nitrile to facilitate deprotonation under mild basic conditions; and (4) divergent transformation of nitrile functionality serves as a useful handle for further elaboration of the reaction products (Scheme 1).

Intensive studies on reaction conditions identified that the combined use of a soft Lewis acidic $[Cu(CH_3CN)_4]ClO_4$/(*R*,*R*)-Ph-BPE complex with a hard Brønsted basic LiOAr exhibited excellent performance in chemoselective activation of allylic cyanides **1**, allowing for the subsequent addition to ketoimines **2** to afford the α-adducts which rapidly isomerized to give α,β-unsaturated nitriles **3** with high enantioselectivity (Scheme 2).[1]

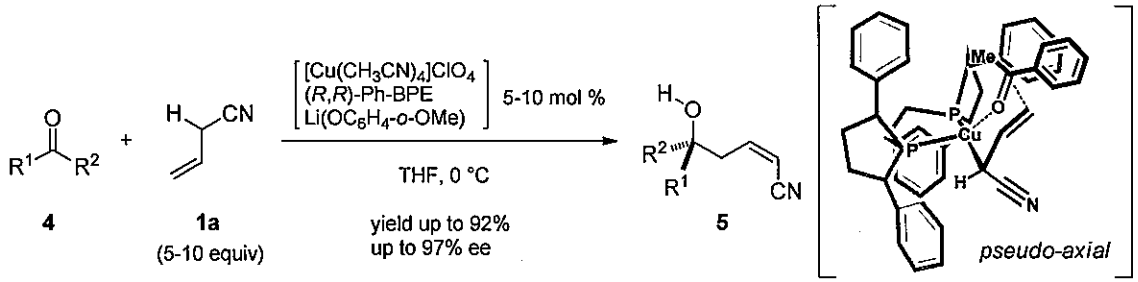
Scheme 2. Direct Catalytic Asymmetric Addition of Allylic Cyanides to Ketoimines



2. Direct Catalytic Asymmetric Addition of Allylic Cyanides to Ketoines

In contrast to the α-addition reaction to ketoimines, the reaction with ketones **4** altered the reaction mode of allyl cyanide **1a** to afford the corresponding γ-adduct **5** exclusively under the same catalyst system, demonstrating that **1** serves as ambident nucluephile (Scheme 3).[2]

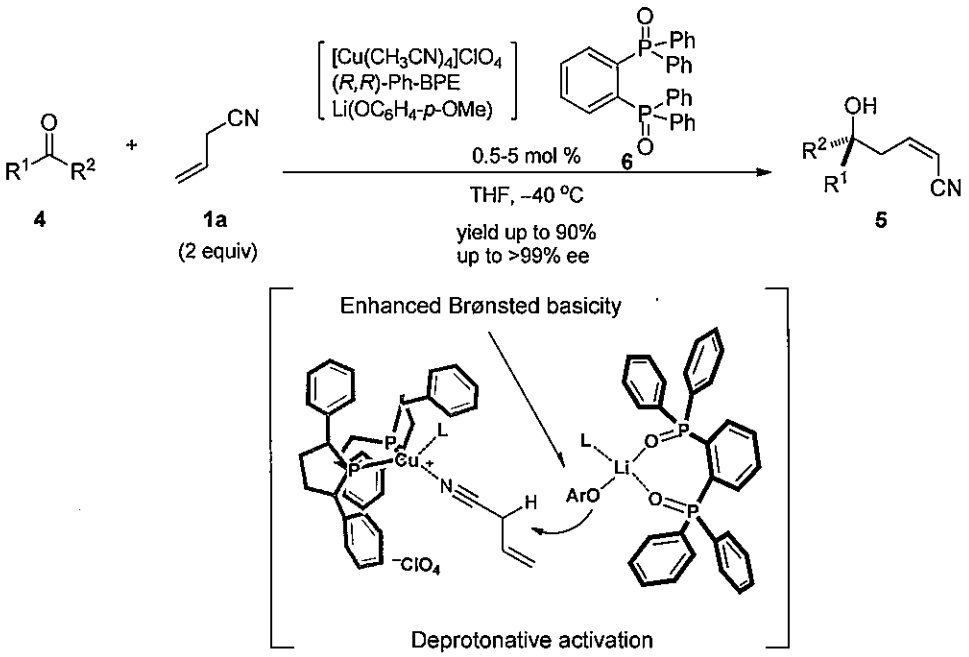
Scheme 3. Direct Catalytic Asymmetric Addition of Allylic Cyanides to Ketones



Although I succeeded in developing direct catalytic asymmetric addition of allylic cyanides **1a** for the construction of tetrasubstituted stereogenic center, relatively high catalyst loading (5-10 mol %) and mandatory use of excess allylic cyanide 1 (5-10 equiv) for satisfactory conversion deflate the

value as the direct catalytic process. To develop more efficient synthetic methodology, detailed mechanistic investigations including kinetic studies in the addition reaction to ketone were conducted and revealed that the rate-determining step is the deprotonation step of allyl cyanide 1a and that the actual Brønsted base is LiOAr, which is in equilibrium with [Cu/(*R*,*R*)-Ph-BPE]ClO_4 and LiOAr. My strategy to accelerate this deprotonation step was employment of a hard Lewis base that would enhance the Brønsted basicity of LiOAr through hard-hard interaction with lithium cation. Addition of the hard Lewis basic phosphine oxide 6 that effectively coordinates to the hard lithium cation enhanced the Brønsted basicity, leading to efficient deprotonative activation under one-tenth the catalyst loading and one-fifth the amount of allyl cyanide **1a** (0.5-1 mol % catalyst loading and 2 equiv of allyl cyanide) (Scheme 4).[3]

Scheme 4. Soft Lewis Acid/Hard Brøsted Base/Hard Lewis Base Cooperative Catalysis

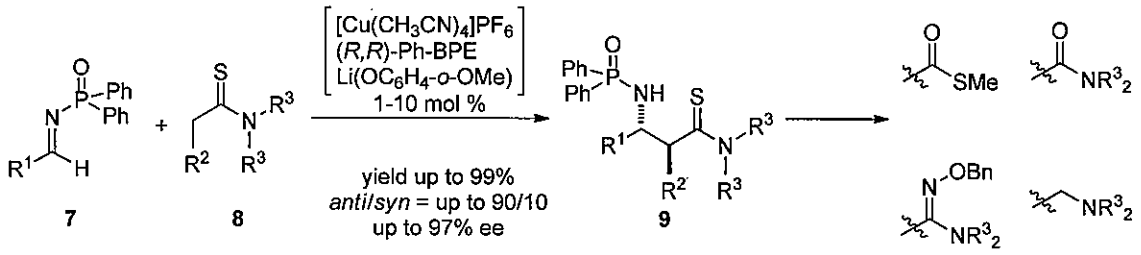


3. Direct Catalytic Asymmetric Mannich-type Reaction of Thioamides

In principle, the soft Lewis acid/hard Brønsted base cooperative catalyst system can be operative for other soft Lewis basic pronucleophiles. I focused on the use of soft Lewis basic thioamides, prepared from corresponding amides with Lawesson's reagents, as carbon pronucleophiles in asymmetric Mannich-type reaction. Thioamides are in carboxylic acid oxidation state and catalytic generation of thioamide enolates remained uncovered due to the lower acidity of α-proton compared with aldehydes and ketones. The same catalyst system comprising [$Cu(CH_3CN)_4$]ClO_4/(*R*,*R*)-Ph-BPE complex with hard Brønsted basic LiOAr turned out to be effective in the reaction of aldimine **7** and thioamides **8** to afford Mannich adduct **9** with relatively high enantioselectivity. Further optimization

of reaction conditions was conducted by me and my coworker, revealing that the reaction can be performed with as little as 1 mol % of catalyst to achieve high enantioselectivity (Scheme 5).[4] The divergent functional group transformation of thioamide functionality into thioester, amide, amine, and amidine highlights the synthetic utility of the products.

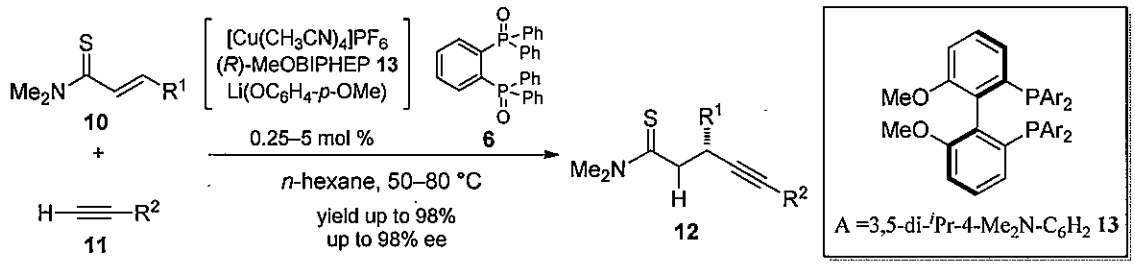
Scheme 5. Direct Catalytic Asymmetric Mannich-type Reaction of Thioamides



4. Direct Catalytic Asymmetric Addition of Terminal Alkynes to α,β-Unsaturated Thioamides

Copper alkynides have been utilized in numerous useful reactions including C(sp)-C(sp^2) coupling reaction such as Sonogashira reaction. In general, copper alkynylides exhibit low nucleophilicity as exemplified by conjugate addition of organocuprates, where alkynes serves as dummy ligands for selective addition of more reactive alkyl groups. I turned my attention to the use of α,β-unsaturated thioamides as electrophilic partner in the direct addition of terminal alkynes. The simultaneous activation of both terminal alkyne and soft Lewis basic α,β-unsaturated thioamide holds promise for overcoming low reactivity of transition metal alkynylide to engage the enantioselective coupling of them under proton transfer conditions. Ligand screening identified that (*R*)-MeO-BIPHEP (**13**) bearing sterically bulky substituents on phosphorous atom and (*R*)-DTBM-Segphos (**14**) matched best for soft Lewis acid/hard Brønsted base catalytic system in catalytic asymmetric conjugate addition of terminal alkynes **11** to α,β-unsaturated thioamides **10**, affording β-alkynyl thioamides **12** in a highly enantioselective manner (Scheme 5).

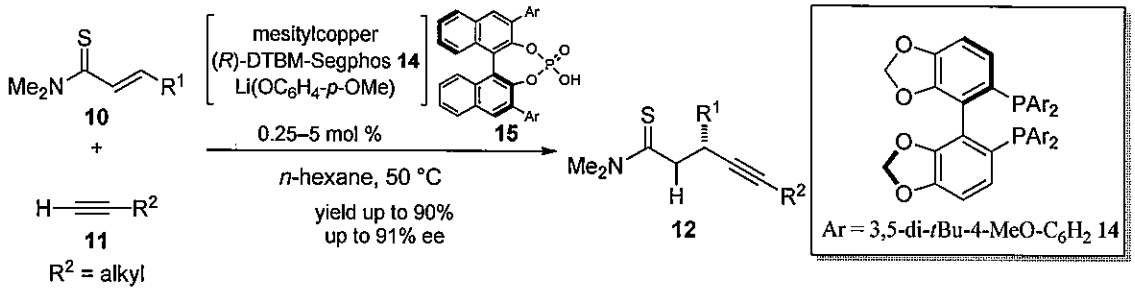
Scheme 5. Direct Catalytic Asymmetric Conjugate Addition of Terminal Alkynes to α,β-Unsaturated Thioamides



The reaction with aliphatic terminal alkynes afforded moderate enantioselectivity even after ligand

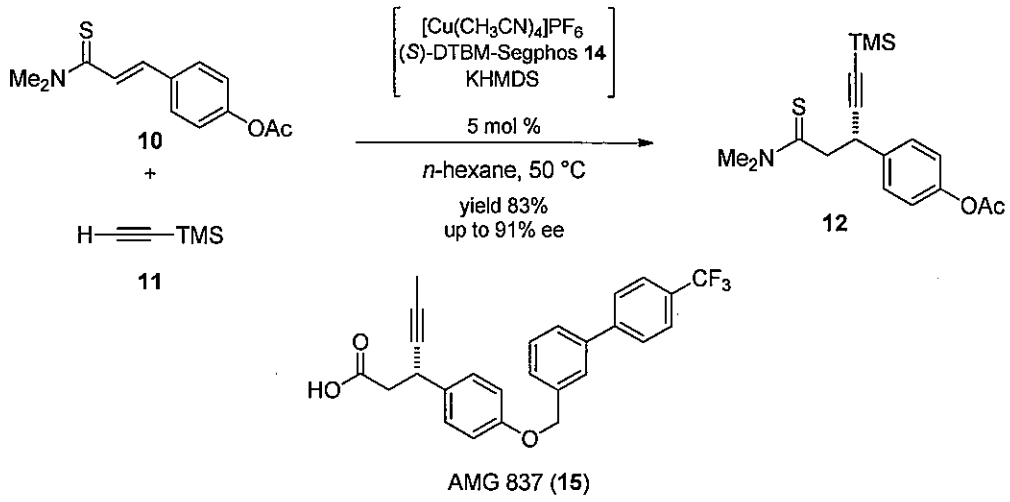
screening, in which the employment of a chiral phosphate anion as an additional stereocontrolling element instead of PF_6^- was beneficial to improve enantioselectivity (Scheme 6).[5]

Scheme 6. Chiral Counteranion Catalysis



Developed catalytic asymmetric conjugate addition reaction was applied for the enantioselective synthesis of potent GPR40 agonist AMG 837 (**15**) employing TMS acetylene as an acetylene equivalent nucleophile (Scheme 7).

Scheme 7. Enantioselective Synthesis of AMG 837.



References

(1) Yazaki, R.; Nitabaru, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 14477. (2) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3195. (3) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 5522. (4) (a) Suzuki, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5028. For a related reaction with aldehyde, see: (b) Iwata, M.; Yazaki, R.; Suzuki, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 18244. (5) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 10275.