Asymmetric Catalysis

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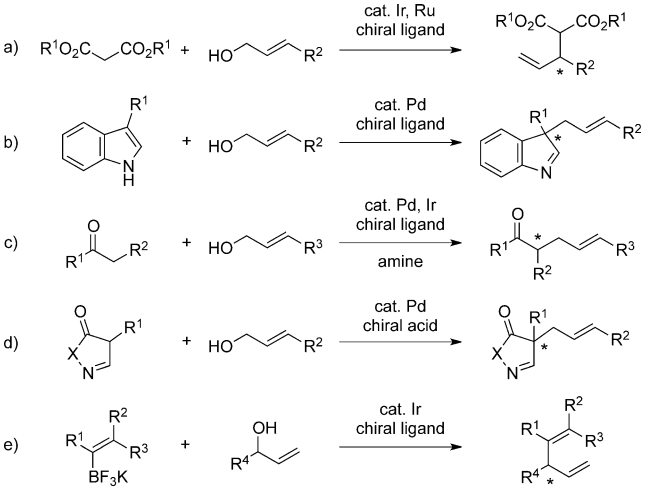
Asymmetric Allylic Alkylation of β-Ketoesters with Allylic Alcohols by a Nickel/Diphosphine Catalyst

*Yusuke Kita, Rahul D. Kavthe, Hiroaki Oda, and Kazushi Mashima**

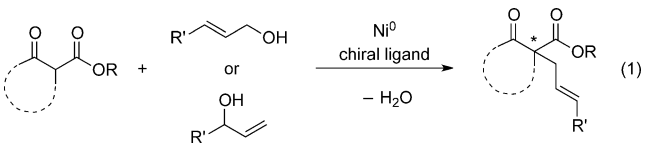
Abstract: *Asymmetric allylic alkylation of β-ketoesters with allylic alcohols catalyzed by [Ni(cod)$_2$]/(S)-H$_8$-BINAP was found to be a superior synthetic protocol for constructing quaternary chiral centers at the α-position of β-ketoesters. The reaction proceeded in high yield and with high enantioselectivity using various β-ketoesters and allylic alcohols, without any additional activators. The versatility of this methodology for accessing useful and enantioenriched products was demonstrated.*

The asymmetric allylic alkylation (AAA) reaction is a highly rational synthetic protocol for constructing stereochemically defined chiral centers,[1] and an asymmetric version of the transition metal assisted nucleophilic substitution of activated allylic compounds, namely the Tsuji–Trost reaction, was developed.[2] Although such catalytic reactions are effective, replacement of activated leaving groups, such as acetates, carbonates, phosphates, and halides, with more synthetically reliable alcohols is required, and the use of allylic alcohols confers several advantages, including 1) high step economy—the preactivation step for preparing activated allylic fragments from allylic alcohols is eliminated, and 2) positive environmental impact—water is generated as the only stoichiometric by-product.[3,4] Because alcohols are poor electrophilic species, however, high catalyst loading, high reaction temperatures, and/or external activators of hydroxy groups are required.[5] In this context, some asymmetric alkylation reactions using allylic alcohols have been reported: β-Diesters were used as nucleophiles in an AAA reaction of allylic alcohols to give allylated products having a chiral center on an allylic moiety (Scheme 1a);[6] 3-subsituted indoles were used in a Friedel–Crafts-type alkylation with allylic alcohols as the alkylating agents (Scheme 1b);[7] α-branched aldehydes and ketones acted as nucleophiles in palladium- and iridium-catalyzed enantioselective allylation assisted by primary or secondary amines (Scheme 1c);[8] Gong and Jiang independently developed an AAA reaction of pyrazol-5-ones and azlactone with allylic alcohols using palladium complexes and chiral phosphoric acids (Scheme 1d);[9] and alkenyl trifluoroborates were also used for asymmetric allylic alkenylation in the presence of iridium/phosphoramidite complexes (Scheme 1e).[10] Despite these advances, however, reactions in which precious metals can be replaced by inexpensive and earth-abundant metals are in high demand.



Scheme 1. Previous reports on transition metal catalyzed AAA reactions using allylic alcohols.

We previously demonstrated that nickel complexes bearing diphosphine ligands exhibit catalytic activity for direct amination of allylic alcohols, in which tetrabutylammonium acetate has remarkable additive effects.[11] This system is highly advantageous for an allylic substitution reaction in terms of low cost, mild reaction conditions, and fact that a hydroxy group activator is not required. The successful application of a nickel/diphosphine system led us to study AAA reactions using a nickel/chiral diphosphine system. We thus focused our attention on β-ketoesters as nucleophiles because of their versatile synthetic intermediacy, however, an activator for the β-ketoesters is normally needed.[12] Herein we report the first nickel-catalyzed AAA reaction of β-ketoesters with allylic alcohols to construct quaternary chiral centers [Eq. (1)].



We initially performed the reaction of the β-ketoester **1a** and allylic alcohol **2a** as model substrates in the presence of 1 mol% [Ni(cod)$_2$], 2 mol% (*S*)-BINAP (**L1**), and 3 Å molecular sieves in Et$_2$O at 25 °C for 36 hours, thus affording the desired product in 91% yield with 70% *ee* (Table 1, entry 1). Only a linear product was obtained, thus suggesting

[*] Dr. Y. Kita, Dr. R. D. Kavthe, H. Oda, Prof. Dr. K. Mashima
Department of Chemistry, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka 560–8531 (Japan)
E-mail: mashima@chem.es.osaka-u.ac.jp

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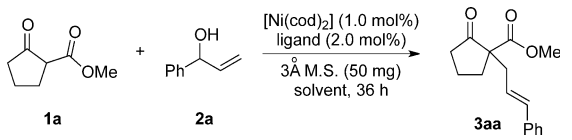
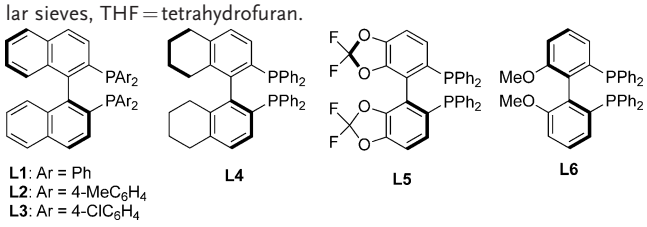
Table 1: Optimization studies of the AAA reaction catalyzed by nickel complexes.[a]



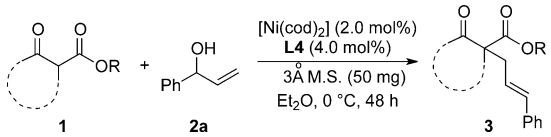
Entry	Ligand	Solvent	T [°C]	Yield [%][b]	*ee* [%][c]
1	**L1**	Et_2O	25	91	70
2	**L2**	Et_2O	25	90	70
3	**L3**	Et_2O	25	60	78
4	**L4**	Et_2O	25	>99	80
5	**L5**	Et_2O	25	40	78
6	**L6**	Et_2O	25	69	74
7	**L4**	Et_2O	10	>99	84
8	**L4**	Et_2O	0	80	87
9[d]	**L4**	Et_2O	0	>99	86
10	**L4**	Et_2O	−10	64[e]	87
11	**L4**	THF	25	50	73
12	**L4**	1,4-dioxane	25	30	60
13	**L4**	DME	25	30	75
14	**L4**	toluene	25	20	64
15	**L4**	$ClCH_2CH_2Cl$	25	20	58
16	**L4**	CH_3CN	25	>99	54
17	**L4**	CH_3NO_2	25	n.d.	–

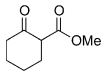
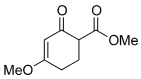
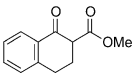
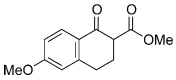
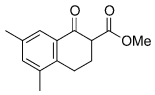
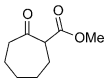
[a] Reaction conditions: A mixture of **1a** (0.75 mmol), **2a** (0.75 mmol), $[Ni(cod)_2]$ (7.5 μmol), ligand (0.015 mmol), 3 Å M.S., and solvent (1.0 mL) was stirred at the indicated temperature for 36 h. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] 2 mol% $[Ni(cod)_2]$ and 4 mol% **L4** was used. Run for 48 h. [e] Average of five runs. cod = 1,5-cyclooctadiene, DME = 1,2-dimethoxyethane, M.S. = molecular sieves, THF = tetrahydrofuran.



that the reaction proceeded via a π-allyl nickel intermediate, as noted in our previous report.[11] This result prompted us to screen a variety of chiral ligands. When using diphosphine ligands bearing an axially chiral biaryl backbone, the reaction proceeded with high enantioselectivity (entries 2–5). In particular, both high yield and high enantioselectivity were achieved in the reaction using (*S*)-H_8-BINAP (**L4**; entry 4). Other types of chiral ligands were not efficient for the present nickel system (see the Supporting Information for details). Other parameters, such as the solvent, temperature, and additive, were optimized (entries 7–17). Among the solvents examined, ether solvents were superior to others, including toluene, dichloroethane, acetonitrile, and nitromethane (entries 4, 11–13). Et_2O gave the best yield (entry 4), whereas THF (entry 11), 1,4-dioxane (entry 12), and DME (entry 13) produced unsatisfactory results. To increase the enantioselectivity, we decreased the reaction temperature, which led to an increased enantiomeric excess of **3aa** (entries 7, 8, and 10). Further optimization studies revealed 2 mol% $[Ni(cod)_2]$ and 4 mol% **L4** in Et_2O at 0 °C for 48 hours to be the optimal reaction conditions (entry 9).

Table 2: Scope of β-ketoesters.[a]



Entry	**1**			Yield [%][b]	*ee* [%][c]
1		R = Et	**1b**	98	82
2		R = *i*Pr	**1c**	97	72
3		R = Bn	**1d**	47	70
4		R = *t*Bu	**1e**	95	14
5			**1f**	91	96
6			**1g**	91	96
7			**1h**	98	95
8			**1i**	91	92
9			**1j**	29	91
10			**1k**	84	34

[a] Reaction conditions: A mixture of **1** (0.75 mmol), **2a** (0.75 mmol), $[Ni(cod)_2]$ (0.015 mmol), **L4** (0.030 mmol), 3 Å M.S., and Et_2O (1.0 mL) was stirred at 0 °C for 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis.

With the optimized reaction conditions determined, we evaluated the AAA reaction of β-ketoesters with the allylic alcohol **2a** (Table 2). Less-hindered substituents on the ester group tended to increase the enantiomeric excess of the products (entries 1–4). In addition, six-membered ketoesters could be used in the reaction. The products of these reactions (**3fa–ja**) were obtained with excellent enantiomeric excess and in good yield (entries 5–8), except for the 5,7-dimethyl-substituted substrate **1j** (entry 9). Although the use of seven-membered nucleophiles also afforded the desired product with good yield, the enantioselectivity was considerably lower (entry 10). Acyclic substrates were allylated with this catalytic system, however, the corresponding product was obtained with a low *ee* value (see the Supporting Information for details).

We next examined the scope with respect to the allyl electrophiles (Table 3). The reaction of a variety of allylic alcohols afforded only the linear product. For aryl-substituted allylic alcohols, the AAA reaction efficiently proceeded at 0 °C to give the corresponding product **3** in high yield and with high enantioselectivity. A variety of electron-donating and electron-withdrawing substituents were tolerated (entries 1–5). In addition, chloro and fluoro groups, which are often used for nickel-catalyzed cross-coupling reactions,[13,14] survived our catalytic conditions (entries 6–8). The *meta*-substituted substrates were also tolerated in the present system (entries 9 and 10). The enantiomeric excess was decreased in reactions

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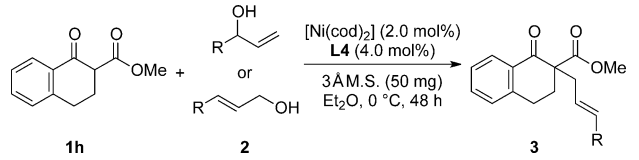
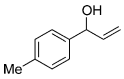
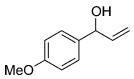
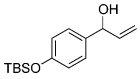
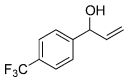
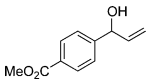
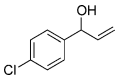
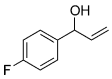
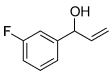
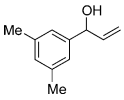
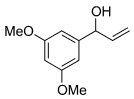
Table 3: Scope of allylic alcohols.[a]



Entry	2		Yield [%][b]	*ee* [%][c]
1		**2b**	93	95
2		**2c**	88	94
3		**2d**	97	92
4		**2e**	95	90
5		**2f**	91	94
6		**2g**	97	93
7		**2h**	97	93
8		**2i**	98	95
9		**2j**	95	93
10		**2k**	98	95
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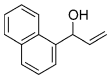
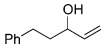
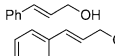
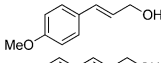
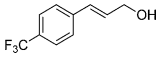
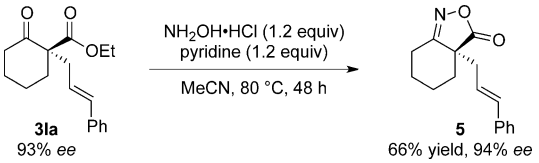
12		**2m**	94	84
13		**2n**	86	94
14		**2o**	96	95
15		**2p**	73	66
16		**2q**	83	66
17		**2a′**	88	94
18		**2c′**	94	93
19		**2e′**	87	89

[a] Reaction conditions: A mixture of **1h** (0.75 mmol), **2** (0.75 mmol), $[Ni(cod)_2]$ (0.015 mmol), **L4** (0.030 mmol), 3 Å M.S., and Et_2O (1.0 mL) was stirred at 0 °C for 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis.

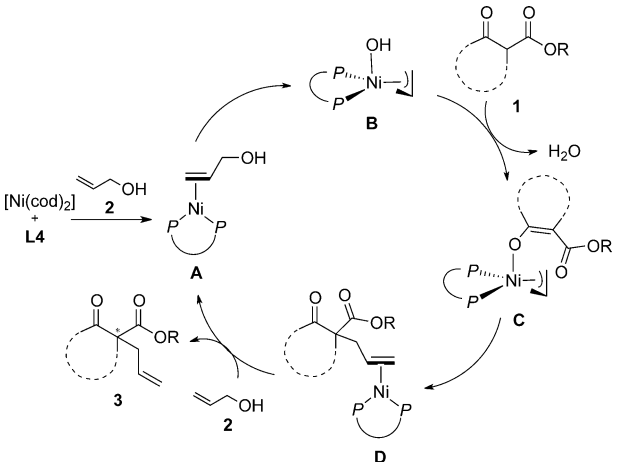
of *ortho*-tolyl and α-naphthyl-substituted allylic alcohols (entries 11 and 12). Moreover, a heteroaromatic-substituted allyl group could be incorporated, thus leading to the furan derivative **3hn** in 86 % yield with 94 % *ee* and the thiophene derivative **3ho** in 96 % yield with 95 % *ee* (entries 13 and 14). Changing the Cα group into an alkyl group led to a high yield of products **3hp** and **3hq** with moderate enantiomeric excess (entries 15 and 16). The $[Ni(cod)_2]$/**L4** system also catalyzed the AAA reaction of linear allylic alcohols to afford the corresponding linear products in high yield with high enantioselectivity (entries 17–19).

Finally, we performed derivatizations of the product obtained from the AAA reaction catalyzed by the Ni/**L4** system [Eq. (2)]. The ketone moiety was reacted with hydroxylamine, followed by cyclization to give the isoxazol-5(4*H*)-one **5**. Such compounds are associated with diverse pharmacologic activities and are also used in dye chemistry.[15] The stereogenic center in the α-position of the carbonyl remained intact during the reaction.



(2)

We propose the mechanism of this reaction to involve a π-allyl nickel intermediate based on our previous report (Scheme 2).[9] Initially, allylic alcohol is oxidatively added to



Scheme 2. Possible mechanism of nickel-catalyzed AAA reaction using allylic alcohols.

a Ni^0/diphosphine complex derived from $[Ni(cod)_2]$ and **L4** to generate the hydroxo π-allyl Ni^{II} complex **B**.[4c,11] The hydroxo ligand abstracts the α proton of the β-ketoester,[16] thus generating complex **C**. It is not clear whether the resulting enolate ligates to Ni^{II} or not. Finally, nucleophilic attack of the enolate affords the product and regenerates the Ni^0/diphosphine intermediate. The lack of a requirement for an activator of β-ketoesters could be attributed to the generation of the hydroxo π-allyl Ni^{II} complex abstracting the α proton of β-ketoesters, because other transition-metal systems normally generate cationic π-allyl metal complexes with the concom-

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itant formation of water by oxidative addition of allyl alcohols.

In summary, we developed an AAA of β-ketoesters using allylic alcohols catalyzed by Ni^0 complexes bearing a chiral diphosphine ligand. The reactions of β-ketoesters proceeded in high yield and with high enantioselectivity, and were compatible with a wide range of functional groups. The present system is highly advantageous in that it requires no activator of nucleophiles. Transformation of one of the products demonstrated the value of the present reaction for rapid generation of functionalized chiral building blocks.

Experimental Section

$[Ni(cod)_2]$ (0.015 mmol, 2.0 mol%), (*S*)-H_8-BINAP (0.030 mmol, 4.0 mol%), and 3Å molecular sieves (50 mg) were added to a 20 mL Schlenk flask in a glove box. Then Et_2O (1.0 mL), allylic alcohol (0.75 mmol), and β-ketoester (0.75 mmol) were added to the reaction mixture under argon. The reaction mixture was stirred at 0 °C for 48 h. Upon reaction completion, the reaction mixture was analyzed by TLC and ^{1}H NMR spectroscopy. The desired product was purified by column chromatography and obtained compound was subjected to HPLC for separation of enantiomer.

Acknowledgments

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Keywords: alkylation · allylic compounds · asymmetric catalysis · enantioselectivity · nickel

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