Nickel-Catalyzed Asymmetric Allylic Alkylation of β-Dicarbonyl Compounds via C-C Bond Activation of 2-Allylated Cyclic 1,3-Diketones

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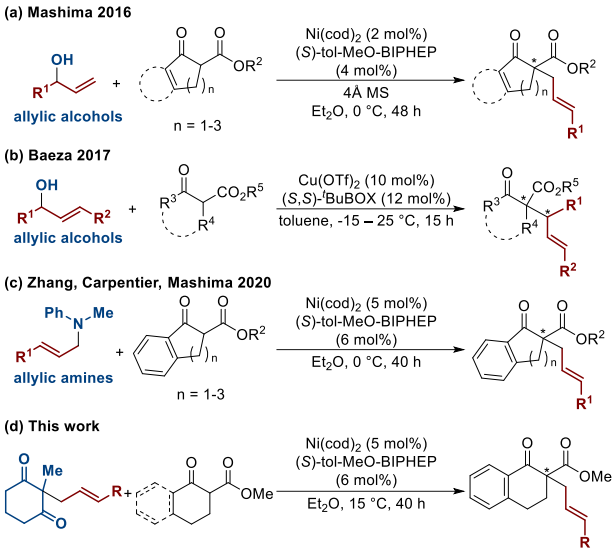
C–C bond cleavage, AAA reaction, nickel, α-allylated-β-dicarbonyl compound, β-ketoester

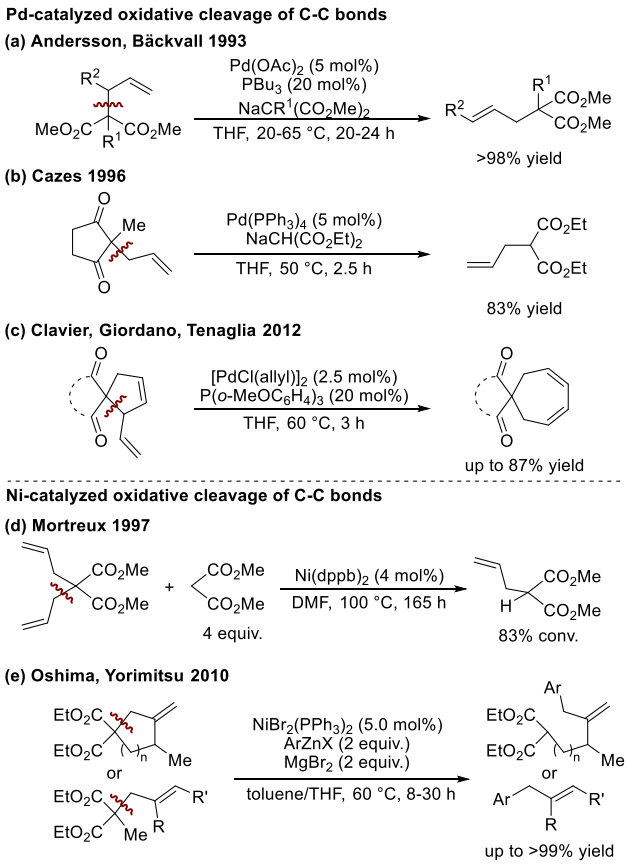
ABSTRACT: The asymmetric allylic alkylation (AAA) reaction using less reactive, stable allylic sources is challenging. We achieved nickel(0)-catalyzed AAA reaction of β-dicarbonyl compounds under ambient conditions through unstrained C–C bond activation of 2-allylated 2-methylcyclohexane-1,3-dione derivatives to afford the corresponding quaternary chiral compounds in high yield with high enantioselectivity. The reaction proceeded almost irreversibly due to the low solubility of the side-product, 2-methylcyclohexane-1,3-dione. Control experiments and DFT calculations allowed for the elucidation the mechanism of the AAA reaction with the Ni(0)-(*S*)-tol-MeO-BIPHEP catalyst system; the turnover limiting step is C–C bond formation, and the reverse reaction requires 4.0 kcal mol^{-1} higher activation energy than the forward reaction.

The asymmetric allylic alkylation (AAA) reaction, known as the asymmetric version of the Tsuji-Trost reaction, is a highly versatile and useful reaction for constructing a chiral quaternary stereogenic carbon center.[1] The most well established system for the AAA reaction is a rational combination of chiral complexes of precious metal, such as Pd, Rh, and Ir as catalyst, with typically activated allylic reagents, such as allyl-halides, -phosphonates, -carbonates, and -acetates to generate π-allyl intermediates. The development of sustainable synthetic protocols using non-precious metals and nonactivated allylic reagents is in high demand. In fact, Cu-,[2] Ni-,[3] and Co-based[4] AAA catalysts have been extensively investigated, but these catalysts require reactive allylic sources. Hence, the use of less-reactive allylic sources for the AAA reaction remains challenging.[5] In 2016, we reported the first AAA reaction using allyl alcohols as a less-reactive allyl source catalyzed by a Ni(0) complex;[6,7] another example reported by Baeza in 2017 was limited to a reaction via nucleophilic addition of chiral Cu-enolate species to allylic alcohols (Scheme 1a and 1b).[8] We also disclosed a Ni-catalyzed AAA reaction utilizing allylic amines as less reactive allylic sources (Scheme 1c).[9] In this context, we focused our attention on the application of α-allylated-β-dicarbonyl compounds as attractive less-reactive, stable allylic sources (Scheme 1d), as some Pd and Ni catalysts are reported to cleave stable allylic C–C bonds of α-allylated-β-dicarbonyl compounds for yielding achiral compounds as shown in Scheme 2.[10-14] Herein, we report the first AAA reaction through an unstrained stable C–C bond cleavage of α-allylated-β-dicarbonyl compounds mediated by a chiral Ni(0) complex;[15] the reaction of a Ni(0) species with an achiral α-allylated-β-dicarbonyl compound initiated the formation of the corresponding π-allyl Ni(II) intermediate, and subsequent nucleophilic attack of a β-ketoester derivative produced the corresponding quaternary chiral compounds in high yield with high enantioselectivity. In addition, we reveal a plausible reaction mechanism based on control experiments and DFT calculations.

Scheme 1. Non-precious Metal-catalyzed AAA Reactions Using Less-reactive Allylic Sources

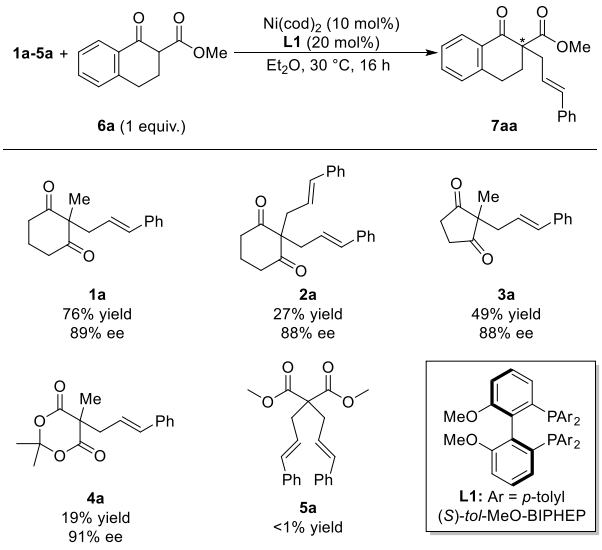


Scheme 2. Examples of Transformation by Using α-Allylated-β-dicarbonyl Compounds as Allylic Sources



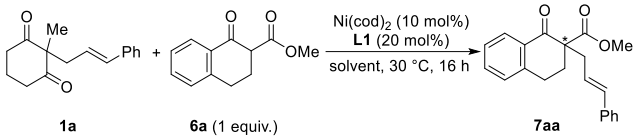
We examined the AAA reaction of methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**6a**) with 2-cinnamyl-2-methylcyclohexane-1,3-dione (**1a**) as a test reaction in the presence of 10 mol% of $Ni(cod)_2$ and 20 mol% of chiral diphosphine ligands. Among the variety screened, we found that (*S*)-tol-MeO-BIPHEP (**L1**) offers the best performance in terms of enantioselectivity (Table S2). Next, we searched for the best allylic source for the AAA reaction of **6a** (Table 1). The use of 2-cinnamyl-2-methylcyclohexane-1,3-dione (**1a**), which includes a cyclic diketone moiety as the leaving group, afforded the corresponding desired product **7aa** in 76% yield with 89% ee; other cyclic diketones, such as 2,2-dicinnamylcyclohexane-1,3-dione (**2a**), 2-cinnamyl-2-methylcyclopentane-1,3-dione (**3a**), and 5-cinnamyl-2,2,5-trimethyl-1,3-dioxane-4,6-dione (**4a**), exhibited lower reactivity with almost the same enantioselectivity. In addition, the AAA reaction with an acyclic allylic source, such as dimethyl 2,2-dicinnamylmalonate (**5a**), which was utilized for Ni-catalyzed allylation reactions by Mortreux,[13] yielded trace amounts of **7aa**. With the allylic source **1a**, we next screened solvents (Table 2). Other ethereal solvents such as THF and CPME decreased the yield of **7aa** down to 14% and 23%, respectively, also with much lower enantioselectivities (entries 2 and 3). When the reaction was carried out in CH_3CN and toluene, **7aa** was obtained in 25% and 16% yields with moderate enantioselectivities, 66% and 76%, respectively. Accordingly, we selected Et_2O as the best solvent.

Table 1. Screening of leaving groups.



Reaction conditions: allylic sources **1a-5a** (0.1 mmol), **6a** (0.1 mmol), $Ni(cod)_2$ (10 mol%), ligand **L1** (20 mol%) in Et_2O (1.0 mL), 30 °C, 16 h. Yield was determined by ^1H NMR analysis using Ph_3CH as an internal standard. ee was determined by HPLC.

Table 2. Screening of reaction solvent.



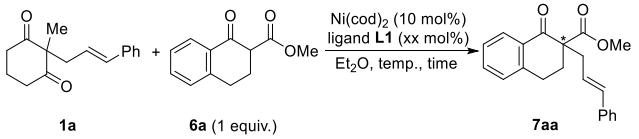
1a **6a** (1 equiv.) **7aa**

entry	solvent	yield [%]	ee [%]
1	Et_2O	76	89
2	THF	14	59
3	CPME	23	74
4	CH_3CN	25	66
5	toluene	16	76

Reaction conditions: **1a** (0.1 mmol), **6a** (0.1 mmol), $Ni(cod)_2$ (10 mol%), ligand **L1** (20 mol%) in Et_2O (1.0 mL), 30 °C, 16 h. Yield was determined by ^1H NMR analysis using Ph_3CH as an internal standard. Ee was determined by HPLC.

Upon using the best allylic source **1a** and solvent (Et_2O), we optimized the reaction conditions using **L1**, and the results are shown in Table 3. Lowering the reaction temperature from 30 °C to 15 °C and 0 °C improved the enantioselectivity up to 92% and 93%, respectively; however, performing the reaction at 0 °C resulted in a low yield (29%) of **7aa** (entries 1-3). Thus, we decided the best reaction temperature as 15 °C, and such the higher temperature slightly reduce the enantioselectivity than our previous report.[6,9] An elongated reaction time (40 h) at 15 °C was necessary to quantitatively produce **7aa** with 90% ee (entry 4). We were able to successfully reduce the ligand loading down to 12 mol% while keeping a quantitative formation of **7aa** (97% isolated yield) with 90% ee (entry 5). Accordingly, the optimized conditions were judged to be as follows: 10 mol% of $Ni(cod)_2$ and 12 mol% of **L1** at 15 °C for 40 h.

Table 3. Optimization of the reaction conditions.



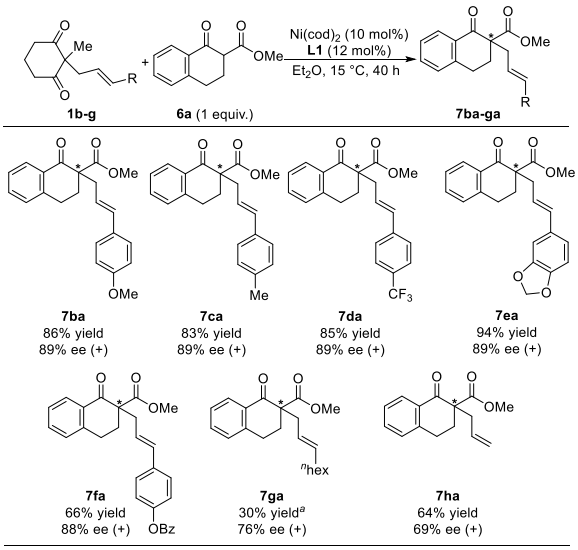
1a **6a** (1 equiv.) **7aa**

entry	temp. [°C]	time [h]	xx [mol%]	yield [%]	ee [%]
1	30	16	20	76	89
2	15	16	20	75	92
3	0	16	20	29	93
4	15	40	20	97	90
5	15	40	12	97 [a]	90

Reaction conditions: **1a** (0.1 mmol), **6a** (0.1 mmol), $Ni(cod)_2$ (10 mol%), in Et_2O (1.0 mL). Yield was determined by ^1H NMR analysis using Ph_3CH as an internal standard. Ee was determined by HPLC. [a]Isolated yield.

Under the optimized conditions, we examined the substrate scope of allylic compounds **1** (Table 4). Both electron-donating and electron-withdrawing groups such as *p*-methoxy (**1b**), *p*-methyl (**1c**), and *p*-trifluoromethyl (**1d**) groups at the *para*-position of the Ph group yielded the corresponding product **7ba**, **7ca**, and **7da** in high yields with high enantioselectivity (86% yield with 89% ee, 83% yield with 89% ee, and 85% yield with 89% ee, respectively). Substrates **1e** and **1f** were compatible with our procedure to give **7ea** and **7fa** in high to moderate yields. When an *n*-hexyl group was introduced in the allylic source (as **1g**), the yield and enantioselectivity of the product **7ga** decreased to 30% and 76%, respectively, while the use of 2-allyl-2-methylcyclohexane-1,3-dione (**1h**) as an allylic source afforded **7ha** in moderate yield with moderate enantioselectivity (69%). These lower ee were probably due to the small substituents of **1g** and **1h**.

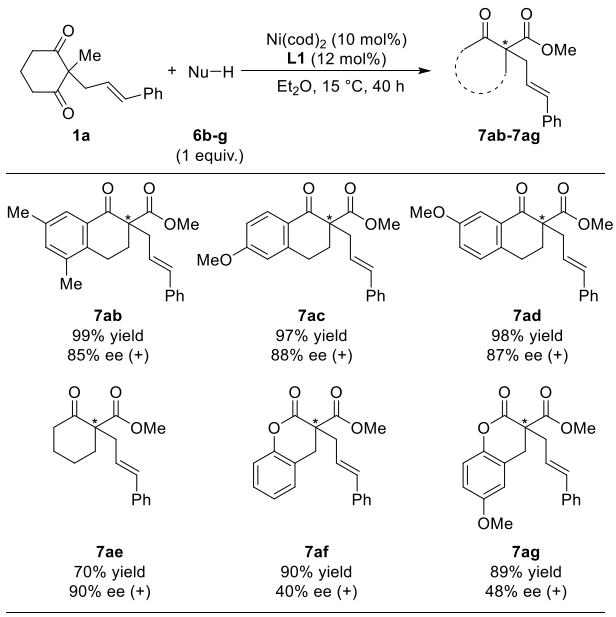
Table 4. Substrate scope of allylic sources.



Isolated yield. [a] Determined by ^1H NMR analysis due to inseparable starting material **6a**.

Next, we explored the substrate scope of β-dicarbonyl compounds **6** (Table 5). β-Ketoester compounds containing 5,7-dimethyl (**6b**), 6-methoxy (**6c**), or 7-methoxy (**6d**) substituents on the tetralone skeleton were competent substrates to give the corresponding products **7ab**-**7ad** in high yields (97-99%) with high enantioselectivities (85-88%). The AAA reaction of methyl 2-oxocyclohexane-1-carboxylate (**6e**) proceeded in a highly enantioselective manner (90% ee), although the yield of **7ae** was moderate (70%). β-Diester compounds **6g** and **6h** were applicable for this reaction as nucleophiles to afford products **7af** and **7ag** in high yields (90% and 89%, respectively), yet with moderate enantioselectivities (40% and 48%, respectively) because the structure of β-diester compounds was not suit for our catalytic system.

Table 5. Substrate scope of β-dicarbonyl compounds.

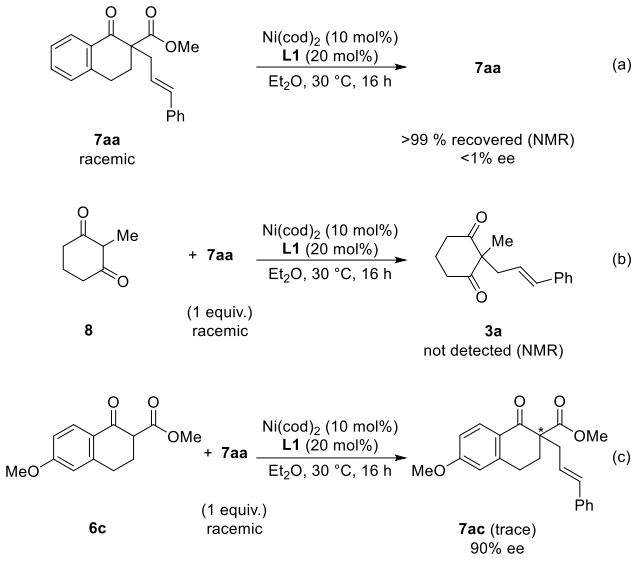


Isolated yield.

To gain insight into the reaction mechanism, we performed a series of control experiments (Scheme 3). When we exposed racemic compound **7aa** to chiral Ni(0)-**L1** complex at 30 °C for 16 h, **7aa** was recovered without any enantio-enrichment (Scheme 3a). The AAA reaction of nucleophile **8** and allylic source **7aa** yielded no product (Scheme 3b). A crossover reaction between **6c** and **7aa** gave only trace amounts of crossover product **7ac**, as detected by GC-MS and HPLC analysis (Scheme 3c). All together, these results suggested that the AAA reaction of **1** and **6** is almost irreversible. In addition, we found that the addition of compound **8** negatively impacted toward catalytic activity of nickel complex and enantioselectivity during the reaction (Scheme S2).

DFT calculations conducted on the model [{(*S*)-tol-MeO-BIPHEP}Ni] catalyst allowed rationalizing a mechanism for these AAA reactions (Figure 1).[16] Ligand exchange between one COD moiety and (*S*)-tol-MeO-BIPHEP gives **int-1**; reaction of the latter with allylic source **1a** reversibly forms **int-2** which is stabilized by 7.4 kcal mol^{-1}. Cleavage of the C–C bond of **int-2** proceeds *via* transition state $\mathbf{TS_{2\text{-}3}}$ with an activation energy of 18.9 kcal mol^{-1} and affords nickel π-allyl complex **int-3** which holds a β-diketonate ligand. Ligand exchange of β-diketonate with β-ketoester **6a** produces **int-4** with compound **8** as a side product. The C–C bond formation step *via* $\mathbf{TS_{4\text{-}5}}$ requires the highest activation energy to yield **int-5**, which is 2.2 kcal mol^{-1} more stable than **int-2**. The low solubility of 2-methylcyclohexane-1,3-dione (**8**: side product) in Et_2O likely shifts the equilibrium to the product side of the AAA reaction (Scheme S1).

Scheme 3. Control Experiments



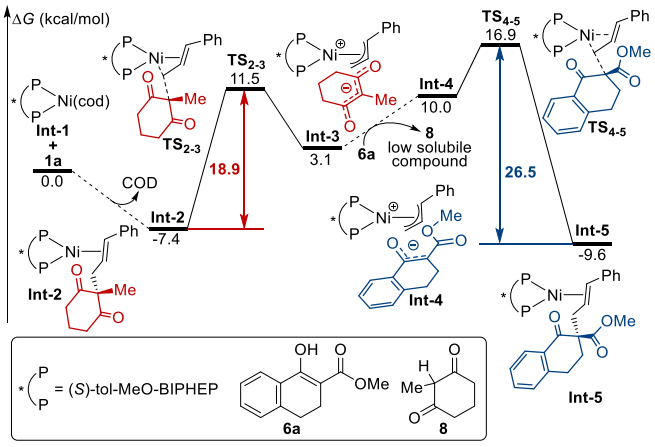


Figure 1. Energy diagram for the AAA reaction through C–C bond cleavage of 1a. Calculations were conducted at M06(SMD)/SDD,6-311+G(2d,p)//M06(SMD)/lanl2dz,6-31+G(d) level of theory.

According to the above control experiments and DFT studies, we propose the reaction mechanism of the Ni-catalyzed AAA reaction using α-allylated-β-dicarbonyl compound in Figure 2. The initial step is coordination of the chiral bisphosphine ligand and C=C double bond of **3** onto $Ni(cod)_2$ to give catalytically active species **A**. C–C bond cleavage at the allyl position yields π-allyl species **B** and a ligand exchange reaction with β-ketoester **7** produces complex **C** along with the poorly soluble (in Et_2O) side-product **8**. The C–C bond formation step **C** → **D** is the turnover limiting step, and ligand exchange follows to afford product **7** and regenerate active species **A**.

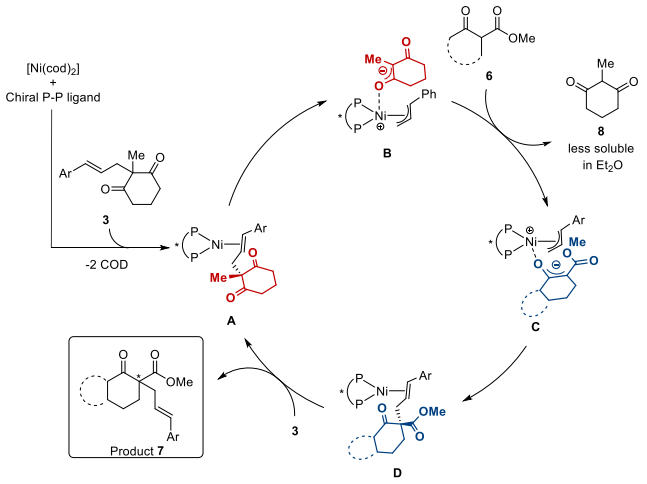


Figure 2. Proposed reaction mechanism.

In summary, we developed an effective AAA reaction using a new allylic source through C–C bond cleavage to give the desired products in high yields with high enantioselectivities. Compared with other α-allylated-β-dicarbonyl compounds, the use of 2-allylated 2-methylcyclohexane-1,3-dione (**3a**) allowed the reaction to proceed under much milder conditions. On the basis of some control experiments, we propose a possible reaction mechanism of the AAA reaction.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge via the Internet at http://pubs.acs.org/.

Experimental procedures and characterization data for all reactions and products, including ^1H and $^{13}C\{^1H\}$ NMR spectra, and HPLC spectra.

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Author Contributions

K.H. and V.S. performed the experiments. K.H. and H.N. performed the DFT calculations. K.H. and H.N. wrote the manuscript under the supervision of J.-F. C. and K.M.

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Nickel-catalyzed Asymmetric Allylic Alkylation