Nickel-Catalyzed Benzylic Substitution of Benzyl Esters with Malonates as a Soft Carbon Nucleophile
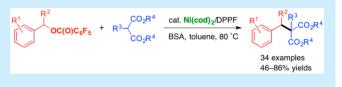
Hiroaki Tsuji,* Keisuke Hashimoto, and Motoi Kawatsura*

Department of Chemistry, College of Humanities & Sciences, Nihon University, Sakurajosui, Setagaya-ku, Tokyo 156-8550, Japan

S Supporting Information

ABSTRACT: The nickel-catalyzed benzylic substitution of benzyl alcohol derivatives with a soft carbon nucleophile is extremely rare compared to that with a hard carbon nucleophile. We have achieved the nickel-catalyzed benzylic substitution of benzyl esters with malonates as a soft carbon nucleophile. Primary and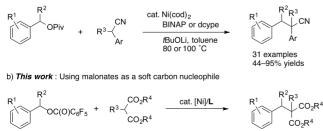 secondary benzyl 2,3,4,5,6-pentafluorobenzoates as well as a wide variety of malonate derivatives were well tolerated in the nickel-catalyzed reaction, providing the corresponding alkylation products in 46−86% yields (34 examples). Additionally, we propose a possible reaction mechanism that would undergo via the η^1- and η^3-benzylnickel intermediates.

The transition-metal-catalyzed benzylic substitution of benzyl alcohol derivatives with carbon nucleophiles offers a useful tool for the formation of carbon−carbon bonds in organic synthesis.[1] The palladium-catalyzed benzylic substitution of benzyl esters with carbon nucleophiles has been thoroughly studied[2] and enabled a number of carbon−carbon bond-forming reactions[3] including their asymmetric variants.[4] As an alternative approach, the nickel-catalyzed benzylic substitution of benzyl ethers and benzyl esters with carbon nucleophiles has been explored in the past decade, and the nickel catalysis provides an efficient method that realizes the benzylic carbon−carbon bond formation.[5] Although various organometallic reagents such as Grignard,[6] organozinc,[7] organoboron reagents,[8] and others[9] have been employed in the reaction systems as a hard carbon nucleophile, the use of a soft carbon nucleophile remains underdeveloped.[10] Chen, Han, and co-workers reported the nickel-catalyzed benzylic alkylation of benzyl esters with arylacetonitriles, providing the corresponding α-alkylated arylacetonitriles in 44−95% yields (Scheme 1a).[11,12] To the best of our knowledge, there is no example for the nickel-catalyzed benzylic substitution of benzyl esters with malonates, even though the reaction would provide an efficient method for the manipulation of malonates
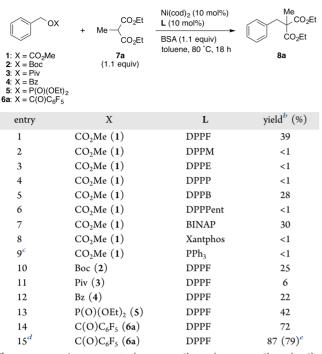
that are one of the important synthetic precursor in organic synthesis.[13] In addition, developing the reaction using a soft carbon nucleophile is considered to be highly desirable in terms of the functional group compatibility. In this context, we report the nickel-catalyzed benzylic substitution of benzyl esters with malonates as a soft carbon nucleophile (Scheme 1b).

We began our investigation with the optimization of the reaction conditions (Table 1). Based on the seminal report by Kuwano and co-workers about the palladium-catalyzed benzylic substitution of benzyl esters with malonates, we initially chose DPPF and bis(trimethylsilyl)acetamide (BSA) as the ligand and the base, respectively.[3c] The reaction of benzyl methyl carbonate (**1**) with diethyl methylmalonate (**7a**) was performed in the presence of Ni(cod)$_2$ (10 mol %), DPPF (10 mol %), and BSA (1.1 equiv) in toluene at 80 °C for 18 h to give the desired alkylation product **8a** in 39% yield (Table 1, entry 1). Based on this initial result, we next tested the other bidentate phosphine ligands (entries 2−8). While the Ni-(cod)$_2$/DPPB or BINAP system exhibited the catalytic activity in the transformation, the reaction with DPPM, DPPE, DPPP, DPPPent, and Xantphos failed to give the desired product. In addition, alkylation product **8a** was not formed using PPh$_3$ as the ligand (entry 9). These results indicated that DPPF (10 mol %) is the most suitable ligand of choice for the nickel catalyst system. To improve the yield of **8a**, we next evaluated the effect of leaving groups of the substrate (entries 10−14). The use of the analogous *tert*-butyl carbonate group (**2**) led to diminished yield (entry 10). The substrates bearing pivalate (**3**) and benzoate (**4**) groups were ineffective for this transformation (entries 11 and 12). We confirmed that benzyl phosphonate **5** displayed similar reactivity to benzyl methyl carbonate (**1**), giving the desired product **8a** in 42% yield

Scheme 1. Nickel-Catalyzed Benzylic Substitution of Benzyl Esters with a Soft Carbon Nucleophile

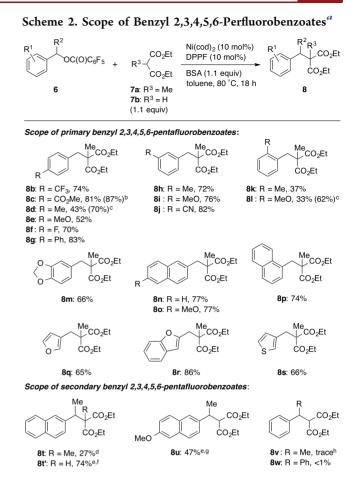a) *Previous example* : Using arylacetonitriles as a soft carbon nucleophile

b) *This work* : Using malonates as a soft carbon nucleophile

Table 1. Optimization of Reaction Conditions[a]

1: X = CO$_2$Me
2: X = Boc
3: X = Piv
4: X = Bz
5: X = P(O)(OEt)$_2$
6a: X = C(O)C$_6$F$_5$

7a (1.1 equiv)

Ni(cod)$_2$ (10 mol%)
L (10 mol%)
BSA (1.1 equiv)
toluene, 80 °C, 18 h

8a

entry	X	L	yield[b] (%)
1	CO$_2$Me (1)	DPPF	39
2	CO$_2$Me (1)	DPPM	<1
3	CO$_2$Me (1)	DPPE	<1
4	CO$_2$Me (1)	DPPP	<1
5	CO$_2$Me (1)	DPPB	28
6	CO$_2$Me (1)	DPPPent	<1
7	CO$_2$Me (1)	BINAP	30
8	CO$_2$Me (1)	Xantphos	<1
9[c]	CO$_2$Me (1)	PPh$_3$	<1
10	Boc (2)	DPPF	25
11	Piv (3)	DPPF	6
12	Bz (4)	DPPF	22
13	P(O)(OEt)$_2$ (5)	DPPF	42
14	C(O)C$_6$F$_5$ (6a)	DPPF	72
15[d]	C(O)C$_6$F$_5$ (6a)	DPPF	87 (79)[e]

[a]Reaction conditions: 1−6a (0.30 mmol), 7a (0.33 mmol), Ni(cod)$_2$ (0.03 mmol), L (0.03 mmol), BSA (0.33 mmol) in toluene (1.2 mL, 0.25 M) at 80 °C for 18 h. [b]The yield was determined by ^{1}H NMR analysis of the crude mixture using phenanthrene as an internal standard. [c]20 mol % of PPh$_3$ was used. [d]The reaction was performed in 0.3 mL of toluene (1 M). [e]Isolated yield.

(entry 13). To our delight, the use of the 2,3,4,5,6-pentafluorobenzoate group was found to be effective as a leaving group, giving the desired alkylation product **8a** in 72% yield (entry 14). Changing the reaction concentration of the reaction from 0.25 to 1 M increased the yield of the desired product **8a** to 87% (79% isolated yield) from 72%.

With the optimized reaction conditions in hand, we investigated the scope of the benzyl 2,3,4,5,6-pentafluorobenzoates **6** using diethyl methylmalonate (**7a**) as a soft carbon nucleophile (Scheme 2). The reactions of **6b** and **6c** having trifluoromethyl and methyl ester groups at the *para* position on their phenyl rings proceeded smoothly to give the desired alkylation products **8b** and **8c** in 74% and 81% yield, respectively. It should be noted that the reaction on a 3 mmol (1.08 g) scale proceeded to afford **8c** in 87% yield. On the other hand, the reactivity of **6d** and **6e** bearing methyl and methoxy groups was lower than that of **6b** and **6c**, resulting in the moderate yields of **8d** and **8e**. The yield of the electron-rich substrate could be improved by increasing the loading amount of the catalyst. For example, the reaction of **6d** in the presence of 20 mol % of Ni(cod)$_2$ and DPPF provided **8d** in 70% yield. Benzyl 2,3,4,5,6-pentafluorobenzoates **6f** and **6g** bearing a fluoro atom and a phenyl group on their aromatic rings underwent the reaction to give the desired alkylation products **8f** and **8g** in 70% and 83% yield, respectively. Both electron-donating (**6h**, **6i**) and -withdrawing (**6j**) substituents at the *meta* position on the phenyl rings were well tolerated to give the corresponding alkylation products **8h−j** in 72−82% yields. The use of **6k** and **6l** bearing *o*-methylphenyl and *o*-methoxyphenyl groups led to diminished yield probably due to the electronic and steric effects of the substituents. When **6l**
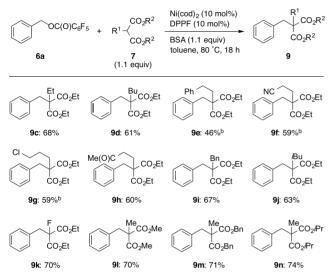
Scheme 2. Scope of Benzyl 2,3,4,5,6-Perfluorobenzoates[a]

6

7a: R^3 = Me
7b: R^3 = H
(1.1 equiv)

Ni(cod)$_2$ (10 mol%)
DPPF (10 mol%)
BSA (1.1 equiv)
toluene, 80 °C, 18 h

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Scope of primary benzyl 2,3,4,5,6-pentafluorobenzoates:

8b: R = CF$_3$, 74%
8c: R = CO$_2$Me, 81% (87%)[b]
8d: R = Me, 43% (70%)[c]
8e: R = MeO, 52%
8f: R = F, 70%
8g: R = Ph, 83%

8h: R = Me, 72%
8i: R = MeO, 76%
8j: R = CN, 82%

8k: R = Me, 37%
8l: R = MeO, 33% (62%)[c]

8m: 66%

8n: R = H, 77%
8o: R = MeO, 77%

8p: 74%

8q: 65%

8r: 86%

8s: 66%

Scope of secondary benzyl 2,3,4,5,6-pentafluorobenzoates:

8t: R = Me, 27%[d]
8t′: R = H, 74%[e,f]

8u: 47%[e,g]

8v: R = Me, trace[h]
8w: R = Ph, <1%

[a]Reaction conditions: **6** (0.30 mmol), **7a** or **7b** (0.33 mmol), Ni(cod)$_2$ (0.03 mmol), DPPF (0.03 mmol), BSA (0.33 mmol) in toluene (0.3 mL) at 80 °C for 18 h. [b]3 mmol (1.08 g) scale. [c]20 mol % of Ni(cod)$_2$ and DPPF were used. [d]2-Vinylnaphthalene was formed in 50% NMR yield. [e]The reaction was performed at 40 °C. [f]2-Vinylnaphthalene was formed in 14% NMR yield. [g]6-Methoxy-2-vinylnaphthalene was detected by GC−MS analyses of the reaction mixture. [h]Styrene was detected by GC−MS analyses of the reaction mixture.

was subjected to the reaction in the presence of 20 mol % of Ni(cod)$_2$ and DPPF, the desired product **8l** was obtained in 62% yield. Substrates **6m−p** having piperonyl and naphthalenyl rings participated in the reaction, furnishing the desired products **8m−p** in good yields. Heterocycles such as furan (**6q**), benzofuran (**6r**), and thiophene (**6s**) were compatible with the reaction system, thus providing the corresponding alkylation products **8q−s** in 65−86% yields. We next carried out the reaction of secondary benzyl 2,3,4,5,6-pentafluorobenzoates.

The reaction of **6t** with diethyl methylmalonate (**7a**) under the optimized reaction conditions afforded the desired product **8t** in 27% yield along with the formation of 2-vinylnaphthalene (50% NMR yield). Fortunately, when diethyl malonate (**7b**) was used as the nucleophile at 40 °C, the formation of 2-vinylnaphthalene could be suppressed, giving the desired alkylation product **8t′** in 74% yield. Secondary benzyl 2,3,4,5,6-pentafluorobenzoate **6u** bearing a methoxy group at the 6 position on the naphthalene ring also underwent the reaction to give **8u** in 47% yield. Unfortunately, the catalyst system did not work well in the reaction of **6v** and **6w** bearing a nonfused aromatic ring with **7b**. We also examined the reaction of benzyl

2,3,4,5,6-pentafluorobenzoates bearing a nitro group and a chloro atom at the *para* position on the phenyl rings. In addition, 3-pyridyl 2,3,4,5,6-pentafluorobenzoate was also subjected to the reaction conditions. However, we could not obtain desired alkylation products.

We next examined the reaction of benzyl 2,3,4,5,6-pentafluorobenzoate **6a** with a wide variety of the malonate derivatives **7** under the optimized reaction conditions (Scheme 3). The reaction of **6a** with diethyl ethylmalonate (**7c**) and
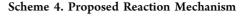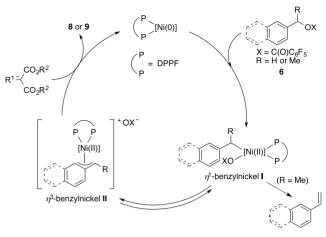
Scheme 3. Scope of Malonate Derivatives[a]

[a]Reaction conditions: **6a** (0.30 mmol), **7** (0.33 mmol), Ni(cod)$_2$ (0.03 mmol), DPPF (0.03 mmol), BSA (0.33 mmol) in toluene (0.3 mL) at 80 °C for 18 h. [b]20 mol % of Ni(cod)$_2$ and DPPF were used.

diethyl butylmalonate (**7d**) afforded the desired alkylation products **9c** and **9d** in 68% and 61% yield, respectively. The reactivity of malonates **7e–g** bearing functionalized linear alkyl chains such as the phenethyl, cyanoethyl, and chloropropyl groups was inferior to that of the other malonates. Therefore, the reaction with these malonates was performed in the presence of 20 mol % of Ni(cod)$_2$ and DPPF to afford the alkylation products **9e–g** in 46–59% yields. Diethyl 2-(3-oxobutyl)malonate (**7h**) reacted with **6a** under the reaction conditions to give the desired product **9h** in 60% yield. Sterically congested malonates such as **7i** and **7j** also participated in the reaction, providing the alkylation products **9i** and **9j** in 67% and 63% yield, respectively. The presence of a fluoro substituent on the active methylene carbon did not affect the alkylation reaction, furnishing the desired product **9k** in 70% yield. Replacement of the ethyl ester groups of the malonate to methyl esters (**7l**), benzyl esters (**7m**), and isopropyl esters (**7n**) did not show any significant influence for the transformation, thus providing the corresponding alkylation products **9l–n** in 70–74% yields. Unfortunately, the other active methylene compounds such as ethyl 2-methylacetoacetate, ethyl benzoylacetate, ethyl 2-cyanopropionate, and ethyl cyanoacetate could not be applicable to the reaction, and the desired alkylation products were not formed.

We propose the possible reaction mechanism for the nickel-catalyzed benzylic substitution of benzyl 2,3,4,5,6-pentafluorobenzoates with malonates as shown in Scheme 4. Initially, benzyl ester **6** would oxidatively add to the nickel (0) species to generate the η^1-benzylnickel intermediate **I**. The formation

Scheme 4. Proposed Reaction Mechanism

of the η^1-benzylnickel intermediate **I** would be supported by the experimental results as follows: the β-hydrogen elimination products were formed during the reaction of secondary benzyl 2,3,4,5,6-pentafluorobenzoates **6t**, **6u**, and **6v** as shown in Scheme 2. The intermediate **I** would isomerize into the η^3-benzylnickel intermediate **II**, and the intermediates **I** and **II** might be in equilibrium.[14,15] Finally, the reaction of the cationic η^3-benzylnickel intermediate **II** with a malonate anion seems to take place to produce the desired alkylation product **8** or **9**. Although the reactivity difference between the benzylnickel species **I** and **II** with a malonate anion is unclear at this stage, we believe that the malonate anion would attack the cationic η^3-benzylnickel **II** based on the detailed mechanistic study of the palladium-catalyzed benzylic alkylation reaction recently reported by Kuwano and co-workers.[16]

In conclusion, we have developed the nickel-catalyzed benzylic substitution of benzyl esters bearing 2,3,4,5,6-pentafluorobenzoate as the leaving group with malonates as the soft carbon nucleophile that is still a rare class of carbon nucleophiles in the nickel catalyst system. The Ni(cod)$_2$/DPPF catalyst system enabled the benzylic substitution of functionalized benzyl 2,3,4,5,6-pentafluorobenzoates with a series of malonate derivatives to provide the corresponding alkylation products in good yields. Although the detailed reaction mechanism is still unclear, we proposed the possible catalytic cycle for the nickel catalysis that would be involved in the η^1- and η^3-benzylnickel intermediates. The nickel-catalyzed benzylic substitution of the promising benzyl esters with the other soft carbon and heteroatom-centered nucleophiles and the detailed mechanistic study are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03475.

Experimental procedures; NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: tsuji@chs.nihon-u.ac.jp.
*E-mail: kawatsur@chs.nihon-u.ac.jp.

ORCID ⊙

Hiroaki Tsuji: 0000-0002-8899-3435
Motoi Kawatsura: 0000-0002-8341-6866

Notes

The authors declare no competing financial interest.

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