Alkohol–Carbonyl Interconversion

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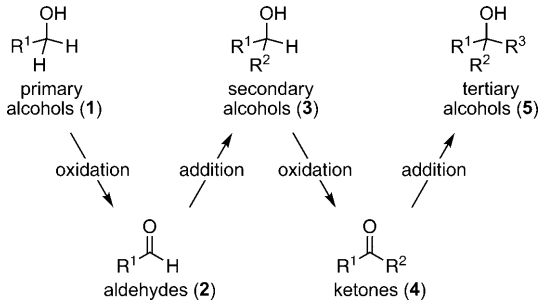
Controlled Alcohol–Carbonyl Interconversion by Nickel Catalysis**

*Takehisa Maekawa, Hiromi Sekizawa, and Kenichiro Itami**

The ability to transform one functional group into another lies at the heart of organic chemistry. Such functional-group interconversions do not involve carbon–carbon bond-forming reactions and are thus seen as less efficient for the construction of complex molecules, however, these interconversions are often critical to "set up" a molecule for such a transformation. The oxidation of primary and secondary alcohols (**1** and **3**) to produce aldehydes (**2**) and ketones (**4**) prior to the addition of organometallic species is a prime example (Scheme 1). Although this reaction is often essential for the subsequent carbon–carbon bond-forming transformation, it does add an extra, linear step to the sequence. Thus, we imagined that performing the two steps, oxidation and addition, together would greatly simplify synthetic routes by essentially eliminating the need to carry out a preliminary oxidation before converting, for example, a primary alcohol (**1**) into a secondary alcohol (**3**), or similarly **3** into a tertiary alcohol (**5**).



Scheme 1. Interconversion of alcohols and carbonyl compounds through oxidation and organometallic addition. The Ni/IPr catalyst described here promotes all possible multistep transformations in one pot (**1**→**3**, **1**→**4**, **1**→**5**, **2**→**4**, **2**→**5**, **3**→**5**).

Numerous practical advantages are associated with such one-pot multistep alcohol–carbonyl interconversions,[1] but a uniform methodology has not been developed, partly because of the incompatibility of the reaction conditions. Whereas alcohol-to-carbonyl transformations are oxidative, the reverse processes such as carbonyl addition reactions are reductive in nature. Herein, we report that $[Ni(cod)_2]$/IPr (cod = 1,5-cyclooctadiene, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) serves as a general catalyst for the controlled one-pot oxidation–addition of alcohols and carbonyl compounds. We demonstrate the feasibility of all possible multistep transformations in alcohol–carbonyl interconversions (Scheme 1). A one-pot nickel-catalyzed synthesis of flumecinol (a hepatic microsomal enzyme inducer) is also described.

As an important progress toward controlled carbonyl–alcohol interconversions, we recently established that the $[Ni(cod)_2]$/IPr catalyst promotes the otherwise difficult intermolecular 1,2-addition of arylboronate esters to unactivated ketones and aldehydes.[2] Among the various arylboron reagents screened, arylboronic acid neopentyl glycol ester ArB(neo) turned out to be the most reactive. The advantage of our [Ni–IPr] catalytic system[2] over other transition-metal-catalyzed organoboron-based 1,2-additions is obvious from the viewpoint of the substrate scope. While other catalytic systems are generally only applicable to aldehydes[3] and some electronically and strain-activated ketones,[4] our [Ni–IPr] catalysis shows good reactivity not only toward aldehydes but also toward diaryl, alkyl aryl, and dialkyl ketones under mild reaction conditions.[2] The high reactivity of our [Ni–IPr] catalyst might be partly due to the unique Ni^0/Ni^{II} mechanism (right-hand catalytic cycle, Scheme 2).

Since many transition-metal complexes are able to mediate the oxidation of alcohols to aldehydes or ketones,[5] we envisioned that our nickel catalysis could be extended to a controlled alcohol–carbonyl interconversion through a one-pot oxidation–addition with an appropriate combination of oxidant and organoboron compound. When identifiying a suitable reagent pair that is capable of achieving this synthetically useful process, we were particularly attracted by the reports of Navarro and co-workers who described the application of $[Ni(cod)_2]$/IPr, which is identical to our organoboronate addition catalyst, in the oxidation of secondary alcohols to ketones by using chlorobenzene (PhCl) as an oxidant and KO*t*Bu as a promoter (left-hand catalytic cycle, Scheme 2).[6–8]

We must stress that the merging of these two catalytic cycles (Scheme 2) is not as straightforward as we initially surmised. At the outset, there are two critical hurdles to overcome for our strategy to provide a synthetically useful protocol for alcohol–carbonyl interconversions: 1) the oxidation of primary alcohols to aldehydes must be achieved (Navarro and co-workers reported that primary alcohols do not undergo oxidation under the conditions that they described)[6] and 2) unwanted side-reactions such as the

[*] T. Maekawa, H. Sekizawa, Prof. Dr. K. Itami
Department of Chemistry, Graduate School of Science
Nagoya University
Chikusa, Nagoya 464-8602 (Japan)
Fax: (+81) 52-788-6098
E-mail: itami.kenichiro@a.mbox.nagoya-u.ac.jp
Homepage: http://synth.chem.nagoya-u.ac.jp

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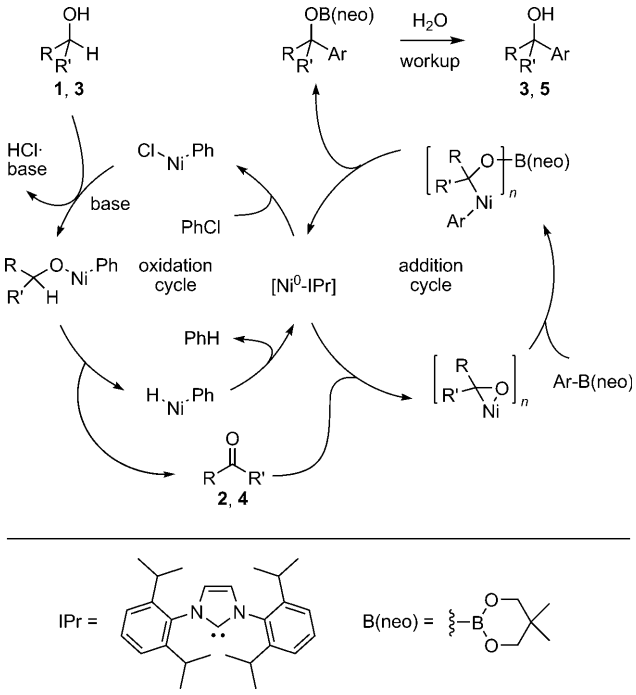
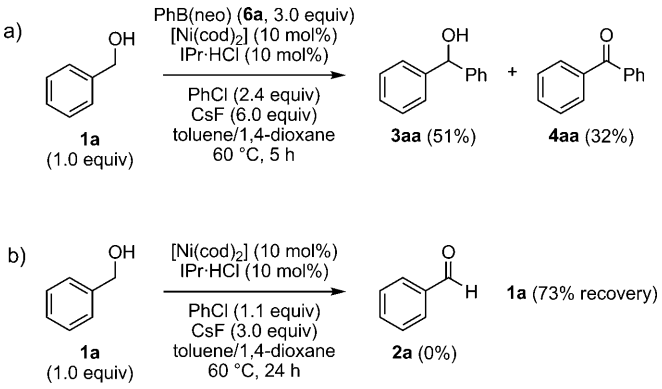


Scheme 2. Nickel catalysis for the interconversion of alcohols and carbonyls.

Suzuki–Miyaura coupling of organoboron species with PhCl must be suppressed.[9]

We first investigated conditions for converting primary alcohols **1** to secondary alcohols **3** through oxidation–addition using a single Ni catalyst. Gratifyingly, we were able to find suitable conditions after extensive screening. The reaction of benzyl alcohol (**1a**, 1.0 equiv) and PhB(neo) (**6a**, 3.0 equiv) in the presence of [Ni(cod)$_2$] (10 mol%), IPr·HCl (10 mol%), PhCl (2.4 equiv), and CsF (6.0 equiv) in toluene/1,4-dioxane at 60°C furnished the desired secondary alcohol **3aa** and ketone **4aa** in 51% and 32% yield, respectively (Scheme 3; see Ref. [10] for details regarding the numbering of compounds). The formation of benzaldehyde (**2a**) was not observed under these conditions. Notably, the formation of biphenyl resulting from the Suzuki–Miyaura coupling of **6a** and PhCl was suppressed under these conditions (<2% yield). The key to this discovery is the use of both a toluene/1,4-dioxane solvent system and an excess of **6a** and CsF. Although the issue of product selectivity (**3aa**/**4aa**) remained to be addressed, we were delighted to observe the feasibility of the desired one-pot process.

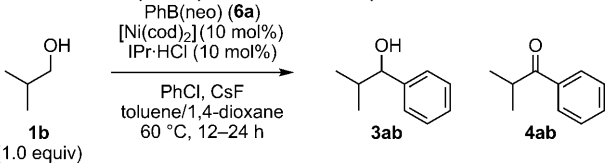


Scheme 3. a) Nickel-catalyzed oxidation–addition of primary alcohol **1a** with PhCl and **6a**. b) Reaction without the boron reagent shows its critical role in the oxidation step.

As already reported by Navarro and co-workers, a system consisting of the [Ni–IPr] catalyst and PhCl cannot oxidize primary alcohols.[6] We confirmed that the reaction of **1a** in the absence of boron reagent **6a** does not give rise to **2a** under our conditions (Scheme 3). Therefore, the arylboronate is likely to play a secondary role in the oxidation of primary alcohols, but its mode of action is debatable and unclear at present.[11]

Nevertheless, with a method for the oxidation–addition of primary alcohols **1** established, we next investigated conditions for making both secondary alcohols **3** and ketones **4** in a controlled manner. The amounts of arylboronate, PhCl, and CsF were examined in greater detail by using the oxidation–phenylation of 2-methylpropanol (**1b**) as a model reaction (Table 1). It was found that secondary alcohol **3ab** could be selectively obtained when **1b** (1.0 equiv) was treated with **6a** (3.0 equiv), PhCl (1.0 equiv), and CsF (4.0 equiv) in the presence of [Ni–IPr] catalyst (10 mol%; Table 1, entry 5).[12,13] Both PhCl and CsF are necessary for this reaction to occur (Table 1, entries 6 and 7). By increasing the amounts of PhCl (2.0–2.4 equiv) and CsF (6.0–10 equiv), ketone **4ab** was produced selectively (Table 1, entries 8 and 9).[13] We also found that phenylboronic acid can be used as an arylating agent in this catalytic reaction (Table 1, entry 10).

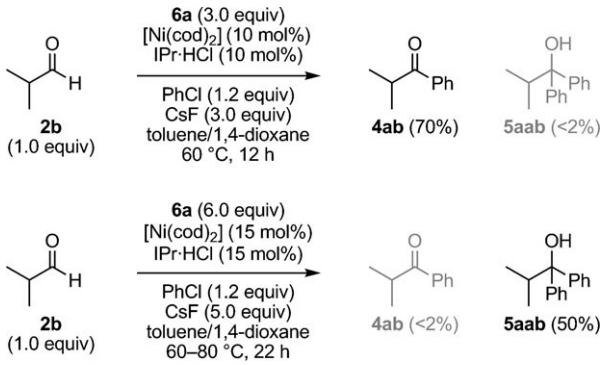
Table 1: Controlled one-pot synthesis of secondary alcohol **3ab** and ketone **4ab** from primary alcohol **1b** and arylboronate **6a**.[a]



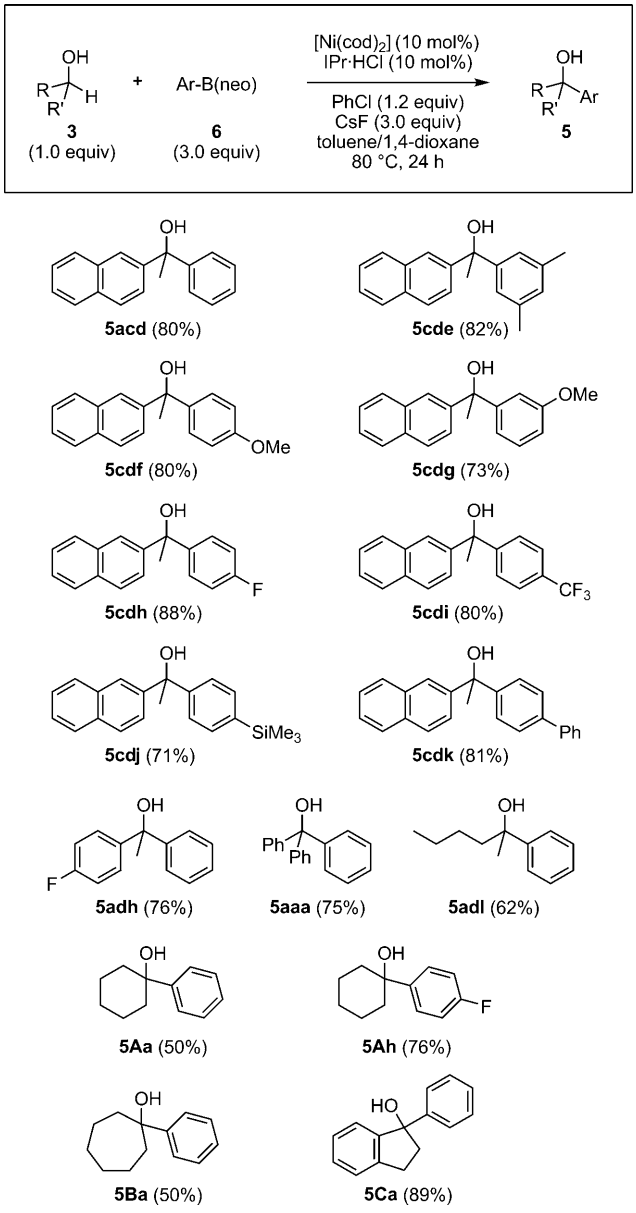
Entry	**6a** [equiv]	PhCl [equiv]	CsF [equiv]	**3ab** [%]	**4ab** [%]
1	1.2	1.2	1.0	12	<5
2	1.2	1.2	4.0	18	14
3	1.2	2.4	4.0	15	11
4	2.0	2.4	6.0	22	32
5	3.0	1.0	4.0	42	0
6	3.0	0	6.0	0	0
7	3.0	1.0	0	0	0
8	3.0	2.0	6.0	0	77
9[b]	3.0	2.4	10	0	83
10[b,c]	3.0	2.4	10	0	74

[a] Conditions: **1b** (0.25 mmol, 1.0 equiv), **6a**, [Ni(cod)$_2$] (25 μmol, 10 mol%), IPr·HCl (25 μmol, 10 mol%), PhCl, CsF, toluene (1 mL), 1,4-dioxane (1 mL), 60°C, 12–24 h. [b] 15 mol% of [Ni(cod)$_2$] and 15 mol% of IPr·HCl were employed. [c] PhB(OH)$_2$ was employed instead of **6a**.

Encouraged by the success of the oxidation–addition and oxidation–addition–oxidation sequences from primary alcohols **1**, we next investigated the addition–oxidation and addition–oxidation–addition sequences from aldehyde **2b**



Scheme 4. Controlled one-pot synthesis of ketone **4ab** and tertiary alcohol **5aab** from aldehyde **2b** and arylboronate **6a**.

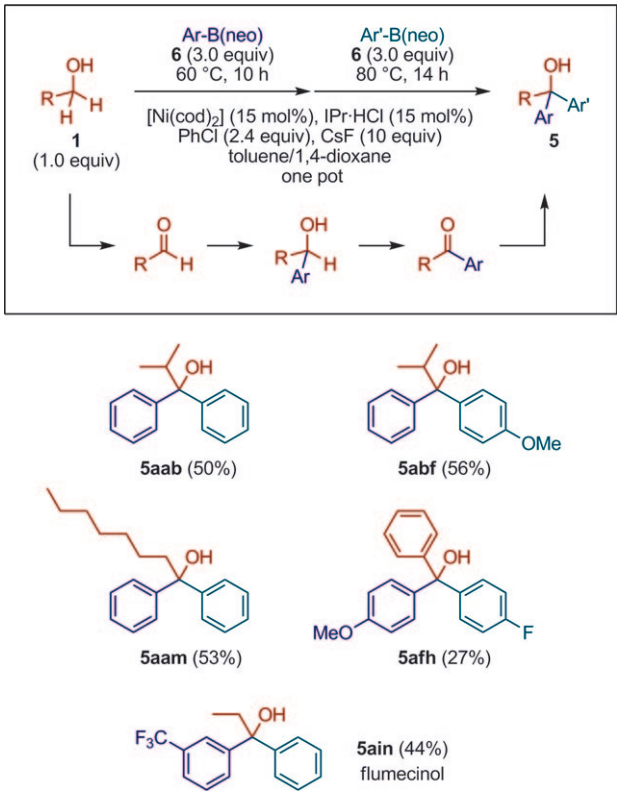


Scheme 5. Controlled one-pot synthesis of tertiary alcohols **5** from secondary alcohols **3** and arylboronates **6**.

(Scheme 4). By adjusting the amounts of phenylboronate **6a**, PhCl, and CsF, both ketone **4ab** and tertiary alcohol **5aab** were selectively synthesized from **2b** in good yields.[13]

We subsequently investigated the two-step oxidation–addition reaction to form synthetically more challenging tertiary alcohols **5** from secondary alcohols **3** (Scheme 5).[10] By tuning the reaction temperature and the amounts of PhCl and CsF, we were able to establish general conditions for this challenging reaction. As shown in Scheme 5, a range of structurally diverse tertiary alcohols **5** can be synthesized in good yields. Aryl alkyl (acyclic and cyclic), diaryl, and dialkyl (acyclic and cyclic) carbinols **3** are all potential substrates for this present nickel-catalyzed reaction. Both electron-rich and electron-deficient arylboronates **6** displayed good reactivity.

As an ultimate one-pot multistep reaction, we finally investigated whether a four-step oxidation–addition–oxidation–addition sequence to produce tertiary alcohols **5** from primary alcohols **1** would be possible with the [Ni–IPr] catalyst (Scheme 6).[10] We also tried to introduce two differ-



Scheme 6. Controlled one-pot synthesis of tertiary alcohols **5** from primary alcohols **1** and arylboronates **6**.

ent aryl groups into the final tertiary alcohol structure by applying two arylboronates **6** in a sequential fashion. Gratifyingly, the following procedure was identified to realize this four-step transformation with reasonable efficiency. A primary alcohol **1** (1.0 equiv) was treated with an arylboronate **6** (3.0 equiv) in the presence of $[Ni(cod)_2]$ (15 mol%), IPr·HCl (15 mol%), PhCl (2.4 equiv), and CsF (10 equiv) in toluene/1,4-dioxane at 60 °C for 10 h to furnish the corresponding arylated ketone **4** in situ.[12] Then, a second arylboronate **6**

(3.0 equiv) was added to the same flask and the resultant mixture was further heated at 80 °C for 14 h. After aqueous workup, the target tertiary alcohol **5** was obtained in reasonable overall yield (Scheme 6).[13] Moreover, to showcase this unprecedented multistep transformation, we successfully demonstrated the one-pot synthesis of flumecinol (**5ain**), a hepatic microsomal enzyme inducer.[14]

In summary, we have developed a general synthetic platform for the interconversion of alcohols and carbonyl compounds in a predictable and controlled fashion in one pot. Under the action of the [Ni–IPr] catalyst, PhCl, CsF, and arylboronates, all possible multistep alcohol–carbonyl interconversions (**1**→**3**, **1**→**4**, **1**→**5**, **2**→**4**, **2**→**5**, **3**→**5**) have been achieved with good overall efficiency.[15] An unexpected role of arylboronates in the oxidation of primary alcohols has been shown. Furthermore, we applied our methodology to the one-pot synthesis of a hepatic microsomal enzyme inducer. These fundamental yet previously unachieved one-pot multistep interconversions of alcohols and carbonyl compounds should greatly streamline chemical syntheses.

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[10] In this study, we used alcohols, carbonyl compounds, and boronates with various substituents. For simplicity, we assigned letters to these substituents: phenyl (**a**), 2-propyl (**b**), 2-naphthyl (**c**), methyl (**d**), 3,5-$Me_2C_6H_3$ (**e**), 4-$MeOC_6H_4$ (**f**), 3-$MeOC_6H_4$ (**g**), 4-FC_6H_4 (**h**), 4-$CF_3C_6H_4$ (**i**), 4-$Me_3SiC_6H_4$ (**j**), 4-PhC_6H_4 (**k**), butyl (**l**), heptyl (**m**), ethyl (**n**). Furthermore, capital letters indicate that the carbon atom at the reaction center was part of a cycle.

[11] We currently assume that the Lewis acid nature of arylboronate (interaction of the boron atom with the oxygen atom of the alcohol) is important in one of the elementary steps of the oxidation catalytic cycle; namely the formation of a nickel alkoxide or the β-hydrogen-elimination step. Related to this assumption, we prepared $PhCH_2OB$(neo) and subjected it to our standard conditions. However, the expected oxidation product (benzaldehyde) was not observed. More extensive mechanistic studies to reveal why arylboronates together with PhCl are necessary for the oxidation of alcohols are currently ongoing.

[12] An excess of arylboronate **6** is completely consumed under these conditions.

[13] High selectivity in product distribution could be explained by the following (assumed) characteristics of the reactions: 1) the four key steps (oxidation of primary alcohol to aldehyde, addition to aldehyde, oxidation of secondary alcohol to ketone, and addition to ketone) each require one equivalent of arylboronate relative

to the substrate; 2) the oxidation step requires one equivalent of chlorobenzene relative to the substrate; 3) arylboronate addition to the ketone requires a reaction temperature of 80 °C; 4) arylboronate decomposes at 60 °C in parallel to its participation in oxidation and addition.

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[15] Other organometallic reagents could be applied in the present multistep alcohol–carbonyl interconversion. While attempts to apply organozinc reagents were so far unsuccessful, some Grignard reagents could be used, for example, in the synthesis of tertiary alcohols from primary or secondary alcohols. However, the carbonyl addition steps are most likely not catalyzed by nickel. Details will be reported in due course.

