Heteroarenes

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# Catalytic Direct-type 1,4-Addition Reactions of Alkylazaarenes

*Hirotsugu Suzuki, Ryo Igarashi, Yasuhiro Yamashita, and Shū Kobayashi**

***Abstract:*** *1,4-addition reactions of alkylazaarenes catalyzed by strong Brønsted bases have been developed for the first time. The desired reactions with α,β-unsaturated amides proceeded under mild reaction conditions to give the 1,4-adducts in high yields. Both ortho- and para-substituted azaarenes afforded the desired adducts in high yields. Regioselective reactions of di- or trimethylpyridine were found to be possible depending on the acidity of the α-hydrogen atoms. Furthermore, a candidate of allosteric protein kinase modulators was synthesized in two steps. An asymmetric variant of this reaction was also found to be feasible.*

Catalytic carbon–carbon (C–C) bond formation is one of the most promising and desired methods for efficient construction of complex carbon frameworks.[1] In particular, Brønsted base catalyzed reactions are ideal from the viewpoint of atom economy because the reactions proceed under simple proton-transfer conditions.[2] To date, many kinds of Brønsted base catalyzed reactions have been developed, however, available pronucleophiles are limited to compounds with relatively acidic hydrogen atoms,[3] such as nitromethane and malonate. The use of carbon pronucleophiles bearing weakly acidic hydrogen atoms ($pK_a$ in DMSO $>35$) in the Brønsted base catalyzed reactions has been considered to be challenging.[4]

Azaarenes, which are heteroaromatics that contain nitrogen atoms in the ring, are common motifs in alkaloid structures. They often show interesting biological activity and typically act through coordination of the nitrogen atoms to the active sites of biomolecules, such as enzymes.[5] For modification of azaarenes, not only direct introduction of substituents on the aromatic parts[6] but also new bond formation at the α-positions of already introduced alkyl substituents on the aromatic rings are useful methods.[7] However, hydrogen atoms at the α-positions are weakly acidic and less reactive. Recently, several transition-metal-catalyzed bond formations through C–H bond activation at the α-positions of alkylazaarenes have been investigated.[8,9] One major strategy is oxidative activation of C–H bonds by using late-transition-metal catalysts,[8] and another approach is activation of C–H bonds by using either a Brønsted or Lewis acid through formation of enamine or enamide species.[9] However, cleavage of inert C–H bonds generally requires high energy, and these reactions are typically conducted under high-temperature reaction conditions. Moreover, regioselectivity is limited in most cases: the α-C–H bond of an alkyl substituent at the *ortho* position relative to the nitrogen atom of the azaarene (e.g., 2-methylpyridine) is activated. Therefore, a new and general reaction system which works under much milder reaction conditions (below room temperature) is highly desired.

We focused on C–C bond-forming reactions of alkylazaarenes by using a strong Brønsted base catalyst under mild reaction conditions. It is known that smooth deprotonation of α-hydrogen atoms of alkylazaarenes occurs even at −78 °C by using strong Brønsted bases such as *n*BuLi.[10] Although C–C bond-forming reactions of alkylazaarenes, using a stoichiometric amount of strong Brønsted base, have been investigated,[11] to our knowledge, Brønsted base catalyzed reactions have not been reported to date. The main issue relates to the difficulty of completing the turnover of strong Brønsted base catalysts because of the weak acidity of the α-hydrogen atoms of alkylazaarenes. We have recently developed an efficient method of catalytic deprotonation for such weakly acidic substrates by using strong Brønsted base catalysts through the generation of strongly basic reaction intermediates.[4c,d,f,12] Herein, we expand this methodology and describe the first example of Brønsted base catalyzed 1,4-addition reactions of a range of alkylazaarenes under mild reaction conditions.

The reaction of 4-methylpyridine (**2a**) with *N*,*N*-dimethylcinnamamide (**1a**) was first conducted in THF at 0 °C in the presence of a catalytic amount of KHMDS (Table 1). 4-Methylpyridine has not often been employed successfully as a substrate in catalytic C–C bond-forming reactions of alkyl azaarenes through C–H activation by using transition-metal catalysts. Contrary to our expectation, deprotonation of the α-hydrogen atom of **2a** was sluggish, and a small amount of the desired product **3aa** was formed together with some side products (entry 1). We then added the crown ether 18-crown-6 to improve the efficiency of the deprotonation. It was found that KHMDS with 18-crown-6 catalyzed the reaction effectively to afford the desired product **3aa** in high yield without any side reaction (entry 2). The effect of the solvent was then examined, and the use of THF was found to give the best result (entries 2–5). Only KHMDS gave the desired product **3aa**, and other bases, including NaHMDS and LiHMDS, did not catalyze the reaction (entries 2 versus 6 and 7). Finally, it was found that the 1,4-addition reaction proceeded well with 5 mol% KHMDS and 18-crown-6 by using a slight excess of **2a** (1.2 equiv; entry 8).

The generality of the reaction with respect to the α,β-unsaturated amide **1** was then investigated under the optimized reaction conditions. The position of the methyl group on the terminal aromatic ring did not affect the reactivity, and the desired product **3** was afforded in good to high yields

[*] Dr. H. Suzuki, R. Igarashi, Dr. Y. Yamashita, Prof. Dr. S. Kobayashi
Department of Chemistry, School of Science, The University of Tokyo
Hongo, Bunkyo-ku, Tokyo (Japan)
E-mail: shu_kobayashi@chem.s.u-tokyo.ac.jp
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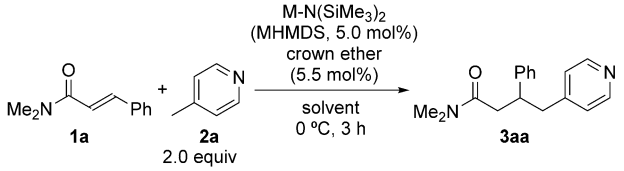
***Table 1:*** Catalytic direct-type 1,4-addition reaction of 4-methylpyridine (**2a**).[a]



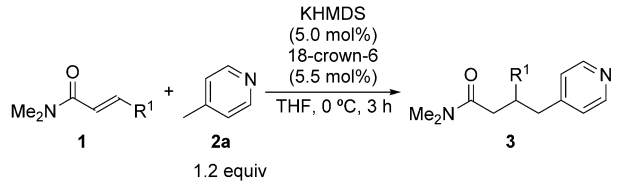

| Entry | MHMDS | Crown ether | Solvent | Yield [%] |
|---|---|---|---|---|
| 1[b] | KHMDS | – | THF | 8[c] |
| 2 | KHMDS | 18-crown-6 | THF | 96 |
| 3 | KHMDS | 18-crown-6 | CPME | 20 |
| 4 | KHMDS | 18-crown-6 | TBME | 40 |
| 5 | KHMDS | 18-crown-6 | toluene | 17 |
| 6 | NaHMDS | 15-crown-5 | THF | n.r. |
| 7 | LiHMDS | 12-crown-4 | THF | n.r. |
| 8[d] | KHMDS | 18-crown-6 | THF | 96 |

[a] The reaction of **1a** (0.40 mmol) with **2a** (0.80 mmol) was performed in a solvent (0.2 M) at 0 °C for 3 h in the presence of a base catalyst prepared from MHMDS (5 mol%) and the crown ether (5.5 mol%) under an Ar atmosphere unless otherwise noted. n.r. = no reaction, HMDS = hexamethyldisilazide, THF = tetrahydrofuran, CPME = cyclopentyl methyl ether, TBME = *tert*-butyl methyl ether. [b] 4-Methylpyridine (4.0 equiv) was used. [c] Yield based on $^1$H NMR spectroscopic analysis. [d] 4-Methylpyridine (1.2 equiv) was used. The concentration of the reaction was 0.4 M.

(Table 2, entries 1–3). The electronic nature of the substituents on the aromatic ring of the α,β-unsaturated amide had some effects, and amides with an electron-rich methoxy group gave the product **3** in similar or slightly higher yield than those with electron-deficient groups (F, Cl, Br; entries 4–7). The use of an α,β-unsaturated amide bearing an electron-rich heteroaromatic 2-furyl ring decreased the reactivity. However, a good yield was obtained by using an increased amount of the catalyst (entry 8). Larger aromatics, 1- and 2-naphthyl, did not hinder the reaction, and the desired products were formed in high yields (entries 9 and 10). Gratifyingly, α,β-unsaturated amides with sterically hindered aliphatic *tert*-butyl and 2-allylpropan-2-yl groups also reacted with **2a** to afford the product in high yield under the optimized reaction conditions (entries 11 and 12). The α,β-unsaturated amide bearing another *N*-alkyl group was also applicable (entry 13).

In our hypothesis, the acidity of the reactive hydrogen atoms on pronucleophiles is key for efficient reactions. The 1,4-addition reaction would proceed smoothly when the p$K_a$ value of the hydrogen atoms (in DMSO) was around 35.[4f] Therefore, we next focused on reactions using other alkylazaarenes bearing weakly acidic α-hydrogen atoms as good pronucleophiles (Table 3). 2-Methylpyridine (**2b**) reacted less readily than 4-methylpyridine (**2a**) to afford the product **3ab**, however, a high yield was obtained when a higher catalyst loading (20 mol%) was used. A related compound, 2,6-dimethylpyridine (**2c**), reacted with **1a** to afford **3ac** under similar reaction conditions. We then focused on regioselective

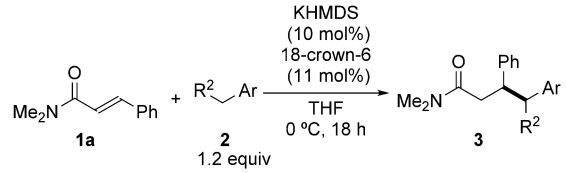
***Table 2:*** Substrate scope of the reaction with respect to α,β-unsaturated amide **1**.[a]

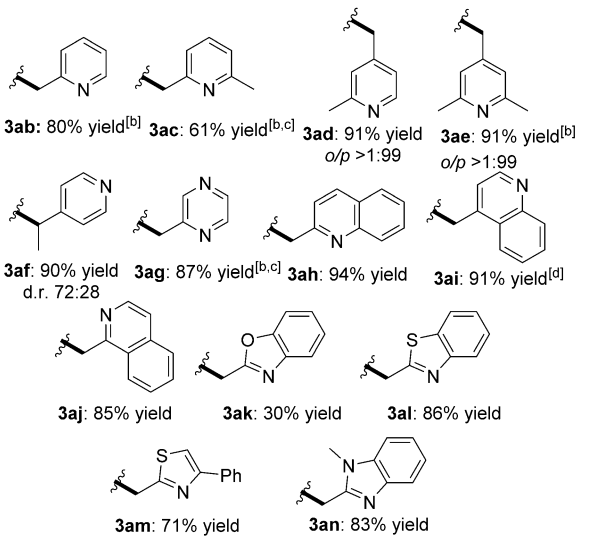



| Entry | $R^1$ | 3 | Yield [%] |
|---|---|---|---|
| 1 | *o*-$MeC_6H_4$ (**1b**) | **3ba** | quant. |
| 2 | *m*-$MeC_6H_4$ (**1c**) | **3ca** | 80 |
| 3 | *p*-$MeC_6H_4$ (**1d**) | **3da** | 89 |
| 4 | *p*-$MeOC_6H_4$ (**1e**) | **3ea** | 98 |
| 5 | *p*-$FC_6H_4$ (**1f**) | **3fa** | quant. |
| 6 | *p*-$ClC_6H_4$ (**1g**) | **3ga** | 61 |
| 7 | *p*-$BrC_6H_4$ (**1h**) | **3ha** | 85 |
| 8[b] | 2-Furyl (**1i**) | **3ia** | 75 |
| 9 | 1-Naphthyl (**1j**) | **3ja** | 91 |
| 10[b,c] | 2-Naphthyl (**1k**) | **3ka** | 95 |
| 11 | *t*Bu (**1l**) | **3la** | 80 |
| 12 | 2-Allylpropan-2-yl (**1m**) | **3ma** | 64 |
| 13 | Ph (**1n**)[d] | **3na** | 86 |

[a] The reaction of **1** (0.40 mmol) with **2a** (0.48 mmol) was performed in THF (0.4 M) at 0 °C for 3 h in the presence of KHMDS (5 mol%) and 18-crown-6 ether (5.5 mol%) under an Ar atmosphere unless otherwise noted. [b] The reaction was conducted with 10 mol% of KHMDS and 11 mol% of 18-crown-6 ether for 18 h. [c] The concentration was 0.13 M. [d] *N*-Cinnamoylpyrrolidine (**1n**) was used as an electrophile.

***Table 3:*** Substrate scope with respect to alkylazaarene **2**.[a]



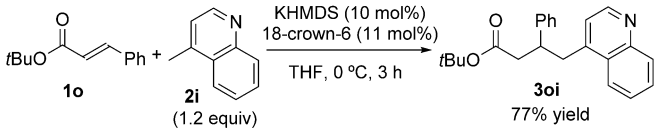

[a] The reaction of **1a** (0.40 mmol) with **2** (0.48 mmol) was performed in THF (0.4 M) at 0 °C for 18 h in the presence of KHMDS (10 mol%) and 18-crown-6 ether (11 mol%) under Ar atmosphere unless otherwise noted. [b] The compound **2** (2.0 equiv), KHMDS (20 mol%), and 18-crown-6 (22 mol%) were used. [c] The reaction was conducted for 20 h. [d] KHMDS (5 mol%) and 18-crown-6 ether (5.5 mol%) were used, and the reaction time was 3 h.

1,4-addition reactions of di- and trialkylpyridines. Given that the acidity of the α-hydrogen atom at the *para*-methyl group of **2a** is higher than that at the *ortho*-methyl group of **2b**,[13] we anticipated that the acidity difference of the α-hydrogen atoms between the *para*- and *ortho*-positions would make regioselective reactions possible. As we expected, both 2,4-dimethylpyridine (**2d**) and 2,4,6-trimethylpyridine (**2e**) reacted selectively at the *para*-position to afford **3ad** and **3ae**, respectively. To our knowledge, these are the first examples of highly *para*-selective catalytic C–C bond-formation reactions using alkylazaarenes.[9c,f,m] When 4-ethylpyridine (**2f**) was used as a pronucleophile, the desired product **3af** was obtained in high yield with good diastereoselectivity.

Other alkylazaarenes were then surveyed (Table 3). 2-Methylpyrazine (**2g**) showed similar reactivity to that of **2b**, and the desired product **3ag** was obtained in high yield by using an increased amount of catalyst. The methylquinolines **2h** and **2i**, and 1-methylisoquinoline (**2j**) were also good pronucleophiles, and the desired products **3ah**, **3ai**, and **3aj** were obtained in high yields with 5 or 10 mol% catalyst loading, even when the methyl group was positioned at the *ortho*-position relative to the nitrogen atom. The KHMDS/crown ether catalyst system was applicable not only to pyridine-type pronucleophiles but also to oxazole-, thiazole-, and imidazole-type compounds. Although 2-methylbenzoxazole (**2k**) showed low reactivity to afford **3ak**, substrates 2-methylbenzothiazole (**2l**), 2-methyl-4-phenylthiazole (**2m**), and 1,2-dimethylbenzimidazole (**2n**) reacted with **1a** well to afford the desired products **3al**, **3am**, and **3an**, respectively, in high yields. Notably, a wide substrate scope with respect to the alkylazaarenes was demonstrated in the catalytic 1,4-addition reactions.

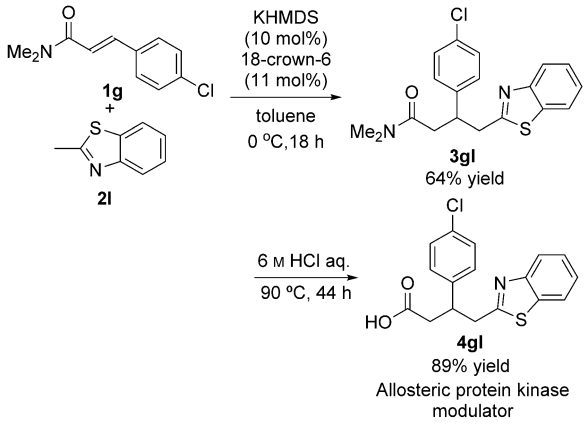
Not only α,β-unsaturated amides but also an α,β-unsaturated ester was successfully employed (Scheme 1). The 1,4-addition reaction of **2i** with *tert*-butyl cinnamate (**1o**) gave the desired product in good yield.



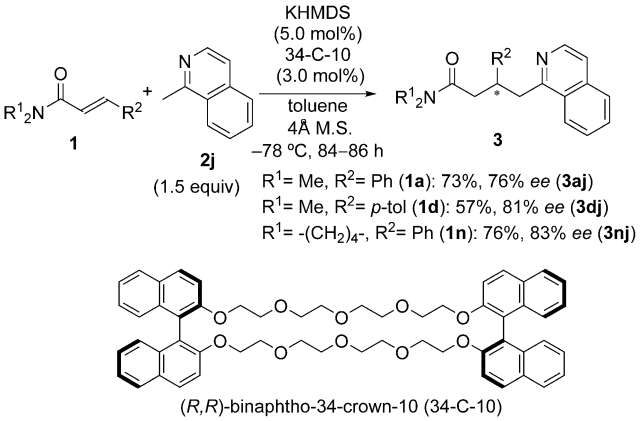

***Scheme 1.*** The catalytic 1,4-addition reaction with α,β-unsaturated ester.

4-Heterocyclic-3-arylbutanoic acids are key structures of allosteric protein kinase modulators.[14] The current catalytic 1,4-addition reaction can provide the main framework of 4-heterocyclic-3-arylbutanoic acids in two steps. As an example, 4-(2-benzothiazolyl)-3-(4-chlorophenyl)butanoic acid (**4gl**) was synthesized (Scheme 2). The desired 1,4-addition reaction proceeded under the optimized reaction conditions, and subsequent hydrolysis afforded the desired compound **4gl** in good yield.

Finally, a preliminary investigation on asymmetric variants of this reaction was conducted (Scheme 3).[15] We have already reported that a chiral macrocyclic crown ether, binaphtho-34-crown-10 (34-C-10), could be used to form an




***Scheme 2.*** Transformation into a biologically active compound.




***Scheme 3.*** Preliminary investigation of catalytic asymmetric 1,4-addition reactions of alkylazaarenes. M.S. = molecular sieves.

effective asymmetric environment around the potassium cation of KHMDS. We have also shown that catalytic asymmetric direct-type 1,4-addition reactions of simple amides, promoted by K/34-C-10, can be achieved with high enantioselectivities.[4c] The catalytic asymmetric 1,4-addition reactions of **2j** were conducted by using KHMDS and 34-C-10, and the desired products were obtained with good to high enantioselectivities. Those results suggest that catalytic asymmetric 1,4-addition reactions of alkylazaarenes were possible under the base-catalyzed reaction conditions. This reaction is the first example of catalytic asymmetric 1,4-addition reaction of non-activated alkylazaarenes with α,β-unsaturated amides.[16–18] Further improvement of the enantioselectivity is ongoing.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** anions · arenes · Brønsted bases · crown compounds · 1,4-addition


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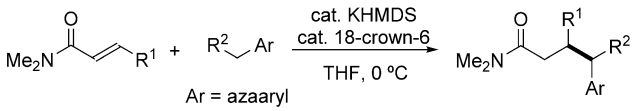
# Communications

**Heteroarenes**

H. Suzuki, R. Igarashi, Y. Yamashita, S. Kobayashi* ——— ■■■■–■■■■

Catalytic Direct-type 1,4-Addition Reactions of Alkylazaarenes




**Going strong**: A strong Brønsted base catalyzes 1,4-addition reactions of alkylazaarenes for the first time. The desired reactions with α,β-unsaturated amides proceed under mild reaction conditions to afford the 1,4-adducts in high yields. KHMDS = potassium hexamethyldisilazide, THF = tetrahydrofuran.