A New Entry of Nucleophiles in Rhodium-Catalyzed Asymmetric 1,4-Addition Reactions: Addition of Organozinc Reagents for the Synthesis of 2-Aryl-4-piperidones

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2-Arylpiperidines are an intensely studied class of compounds due to their biological activity as well as their synthetic utility.[1,2] For example, a subclass of the tachykinin antagonists has a common structural motif based on a 2-arylpiperidine moiety as shown in Figure 1 (**A** and **B**).[3,4] Compound **B**, developed by Glaxo Group Ltd., UK, has a strong affinity with the NK1 receptor (one of the three types of tachykinin receptors identified) and is particularly useful for the treatment or prevention of depressive states and/or anxiety.[4] As a consequence of the significance of these compounds, the development of efficient methods for their enantioselective synthesis is an important objective, but most of the existing methods rely on the use of a stoichiometric amount of chiral reagents.[5] In contrast, very few catalytic enantioselective routes to the synthesis of 2-arylpiperidines have been reported.[6]
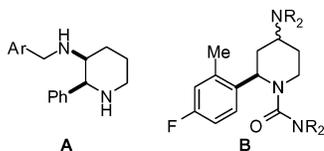
Figure 1. Examples of tachykinin antagonists.

To remedy this methodological deficiency, we envisioned that these compounds can be rapidly synthesized by asymmetric 1,4-addition of organometallic reagents to 2,3-dihydro-4-pyridones (e.g., **1** in eq 1),[7] followed by a reduction of the carbonyl group.[8] In this Communication, we describe the development of a rhodium-catalyzed highly enantioselective synthesis of 2-aryl-4-piperidones (**2**) by the use of organozinc reagents (eq 1), which consist of a new type of nucleophiles in the 1,4-addition reactions by rhodium catalysis.[9]
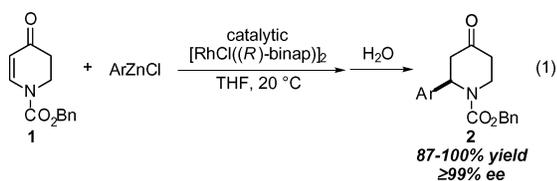
In the past few years, we have focused on the development of a rhodium-catalyzed asymmetric 1,4-addition of organoboron reagents to a variety of α,β-unsaturated compounds.[10] On the basis of these successes, we initially investigated the reaction of **1** with PhB-(OH)$_2$ in the presence of 3 mol % Rh(acac)(C$_2$H$_4$)$_2$/(R)-binap at 100 °C (Table 1, entry 1). Unfortunately, these reaction conditions, which are highly effective for the asymmetric 1,4-addition to 2-cyclohexen-1-one,[10a] proved only moderately effective for the formation of **2a** (33% yield), suggesting that compound **1** has relatively low reactivity toward 1,4-addition, although the enantioselectivity was high (96% ee). The use of [Rh(OH)((R)-binap)]$_2$ as the catalyst improved the reactivity to some extent (entry 2; 78% yield),[11,12] while the use of Ph-9-BBN as the nucleophile in an aprotic solvent did not (entry 3; 33% yield).[13]

Table 1. Survey of Nucleophiles in the Rhodium-Catalyzed 1,4-Addition to **1**

entry	Ph–M (equiv)	condition[a]	yield (%)[b]	ee (%)
1	PhB(OH)$_2$ (3.0)	A	33[c]	96
2	PhB(OH)$_2$ (3.0)	B	78[d]	98
3	Ph-9-BBN (1.1)	C	33[e]	97
4	PhTi(Oi-Pr)$_3$ (1.6)	D	~70[f]	>99.5
5	PhZnCl (1.5)	E	95	>99.5

[a] Condition A: Rh(acac)(C$_2$H$_4$)$_2$/(R)-binap, dioxane/H$_2$O (10/1), 100 °C, 2 h. Condition B: [Rh(OH)((R)-binap)]$_2$, dioxane/H$_2$O (10/1), 50 °C, 5 h. Condition C: [Rh(OMe)(cod)]$_2$/(R)-binap, toluene, 80 °C, 1 h; then MeOH quench. Condition D: [Rh(OH)((R)-binap)]$_2$, THF, 20 °C, 1 h; then MeOH quench. Condition E: [RhCl((R)-binap)]$_2$, THF, 20 °C, 2 h; then H$_2$O quench. [b] Isolated yield. [c] 35% conversion of **1** with complete consumption of PhB(OH)$_2$. [d] 83% conversion of **1** with complete consumption of PhB(OH)$_2$. [e] 33% conversion of **1**. [f] Full conversion of **1** to a ~3/1 mixture of 1,4-adduct/1,2-adduct.

We then explored a different type of organometallic reagent as the nucleophile and employed PhTi(Oi-Pr)$_3$ as we recently described in the 1,4-addition to α,β-unsaturated ketones.[14] Under these conditions, product **2a** was obtained in ~70% yield along with the undesired 1,2-addition product (entry 4; 1,4-adduct/1,2-adduct ~3/1). This observation also points out the lack of proper reactivity in compound **1**, because the 1,2-addition of PhTi(Oi-Pr)$_3$ proceeds smoothly in the absence of a rhodium catalyst. After some investigations, however, we were able to find that the use of PhZnCl dramatically improves the reactivity under mild conditions, giving the desired product **2a** in 95% yield with an excellent ee of >99.5% (R)[15] (entry 5).

It is worth noting that the scope of the catalytic asymmetric 1,4-addition of organozinc reagents to **1** is fairly broad: the process

Table 2. Scope of Organozinc Reagents in the Rhodium-Catalyzed Asymmetric 1,4-Addition to **1**

entry	Ar	product	yield (%)	ee (%)
1	Ph	**2a**	95	>99.5
2	4-PhC$_6$H$_4$	**2b**	97	>99.5
3[a]	4-MeOC$_6$H$_4$	**2c**	90	99
4	4-FC$_6$H$_4$	**2d**	91	>99.5
5[a]	3,5-Me$_2$C$_6$H$_3$	**2e**	87	99
6[a]	2-MeC$_6$H$_4$	**2f**	100	99

[a] 3.0 equiv of ArZnCl was used in the presence of 6 mol % Rh.

tolerates a sterically and electronically diverse array of arylzinc reagents, giving the products uniformly in good yields with excellent enantioselectivities (Table 2; **2a**−**2f**, 87−100% yield, ≥99% ee (*R*)).[16]

This 1,4-addition method can also be applied to the preparation of key intermediate **3** for the synthesis of tachykinin antagonists **B** (Figure 1).[4] Thus, the reaction of **1** with 4-fluoro-2-methylphenyl-zinc chloride in the presence of a catalytic amount of [RhCl((*R*)-binap)]$_2$, followed by the removal of the benzyloxycarbonyl group, efficiently affords compound (*R*)-**3** in high yield and ee (eq 2; 73% yield in two steps, 97% ee).
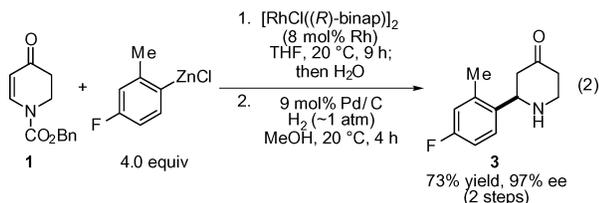
Because zinc enolates (e.g., **4**) are the primary products in these 1,4-additions of organozinc reagents, they could be further functionalized in one-pot by the addition of electrophiles to the reaction mixture. For example, the addition of allyl bromide provides α-allylated product **5** as a single diastereomer in the trans-form with high yield (eq 3; 83% yield). The use of pivaloyl chloride as the electrophile, however, affords O-acylated product **6** in excellent yield (97% yield).

The utility of the asymmetric 1,4-addition of organozinc reagents catalyzed by Rh(I)/(*R*)-binap is not limited to the enantioselective synthesis of 2-aryl-4-piperidones. Thus, both cyclic and acyclic α,β-enones can be enantioselectively arylated under these conditions, giving β-chiral ketones (**7** and **8**) in excellent yield and enantioselectivity as well (eqs 4 and 5; 98−99% yield, 94−99% ee).
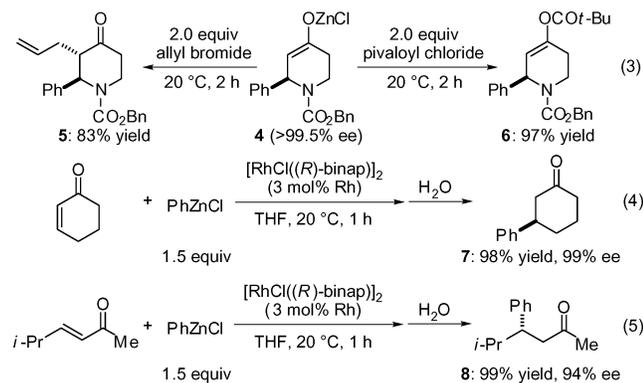
In summary, we have described that a rhodium-catalyzed 1,4-addition reaction can be used to prepare synthetically and biologically important 2-aryl-4-piperidones efficiently with very good enantioselectivity by employing organozinc reagents as the nucleophilic component. This method has then been applied to the enantioselective synthesis of the key intermediate of tachykinin antagonists. The utility of this process has been further demonstrated both by the electrophilic quench and by the employment of other α,β-unsaturated substrates. Future studies will explore further use of these versatile nucleophiles, organozinc reagents, in rhodium-catalyzed 1,4-addition and other related reactions.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The absolute configuration of the 1,4-adducts was assigned to be (*R*), based on the optical rotation of compound **3** in eq 2 (see Supporting Information).

(16) Under our standard conditions, alkyl- or alkenylzinc reagents are not suitable nucleophiles.

JA048825M