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Rhodium-Catalyzed Asymmetric 1,4-Addition of Sodium Tetraarylborates to β,β-Disubstituted α,β-Unsaturated Esters

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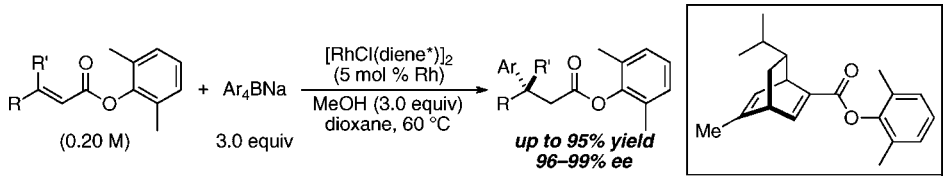
ABSTRACT



A rhodium-catalyzed 1,4-addition of sodium tetraarylborates to β,β-disubstituted α,β-unsaturated esters has been developed. Highly efficient asymmetric catalysis has also been described to create quaternary carbon stereocenters at the β-position of esters by tuning the ester group of substrates and employing a readily available chiral diene ligand.

Catalytic asymmetric 1,4-addition of organometallic reagents to β,β-disubstituted α,β-unsaturated compounds has been extensively investigated in the past few years for the efficient construction of all-carbon quaternary stereocenters.[1] Most widely employed substrates in this regard are α,β-unsaturated ketones under copper[2] or rhodium[3] catalysis, and several other reactive substrates such as nitroalkenes,[4] α,β-unsaturated pyridyl sulfones,[5] and 3-substituted maleimides[6] have also been utilized. In contrast, although β-chiral esters would be synthetically more useful, the use of β,β-disubstituted α,β-unsaturated esters has been much less explored, presumably because of their inherently lower reactivity as electrophiles. As a consequence, only alkylidene Meldrum's acids, highly activated diesters, have been successfully employed to date.[7] In this context, herein we describe the development of rhodium-catalyzed 1,4-addition of air-stable sodium tetraarylborates to β,β-disubstituted α,β-unsaturated esters,

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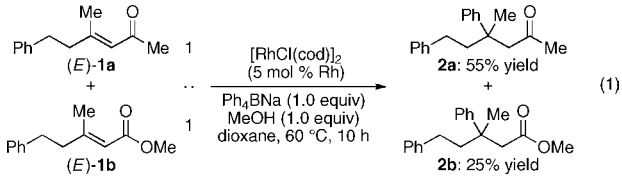
where high enantioselectivity can be achieved by employing a readily available chiral diene ligand.

Recently, we described that sodium tetraarylborates can function as effective nucleophiles for the rhodium/diene-catalyzed 1,4-addition reactions to β,β-disubstituted α,β-unsaturated ketones, where other typical organoboron nucleophiles such as arylboronic acids completely fail.[3a] To assess the reactivity difference between β,β-disubstituted unsaturated ketones and esters, we initially conducted a control experiment by employing enone (*E*)-**1a** (1.0 equiv) and enoate (*E*)-**1b** (1.0 equiv) in the rhodium/cod-catalyzed 1,4-addition of sodium tetraphenylborate (1.0 equiv) in methanolic dioxane at 60 °C (eq 1). Under these conditions, ketone product **2a** and ester product **2b** were obtained in 55% and 25% yield, respectively, indicating that β,β-disubstituted enoate **1b** is significantly lower in reactivity than enone **1a**.

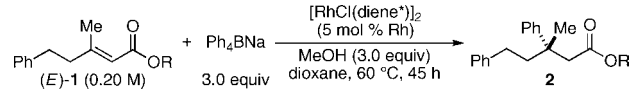


(1)

Keeping this result in mind, we examined several reaction conditions using (*E*)-**1b** and sodium tetraphenylborate and found that a reaction with 3.0 equiv of sodium tetraphenylborate under the catalysis of $[RhCl(cod)]_2$ (5 mol % Rh) in the presence of 3.0 equiv of MeOH in dioxane proceeded at 60 °C with moderate efficiency to give 1,4-adduct **2b** in 60% yield (Table 1, entry 1).[8] In contrast, product **2b** was not obtained at all in the presence of $[RhCl(binap)]_2$[9] as a catalyst or by the use of other typical phenylboron nucleophiles such as phenylboronic acid, phenylboroxine, phenylboronic acid neopentylglycol ester, and potassium phenyltrifluoroborate.

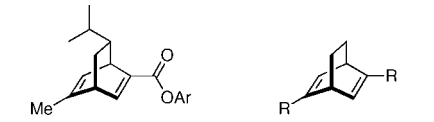
Fortunately, while developing an asymmetric variant of this process, we discovered that a rhodium complex coordinated with ester-attached chiral diene (*R*)-**L1**[10] displayed activity higher than that of $[RhCl(cod)]_2$, giving **2b** in 79% yield with 76% ee (entry 2). In the presence of $[RhCl((R)\text{-}\mathbf{L1})]_2$, both yield and ee were further improved by changing the substrate to *tert*-butyl ester (*E*)-**1c** (84% yield, 89% ee; entry 3) and to 2,6-dimethylphenyl ester (*E*)-**1d** (93% yield, 97% ee; entry 4).[11] We subsequently found that even higher enantioselectivity could be achieved through modification of the chiral diene ligand to (*R*)-**L2**[10] (99% ee; entry 5). Conventional C_2-symmetric chiral dienes such as (*R*,*R*)-Bn-bod*[12] and (*R*,*R*)-Ph-bod*[12,13] also exhibited similarly high efficiency (91−94% yield, 97−98% ee; entries 6 and 7).[14]

Table 1. Rhodium-Catalyzed 1,4-Addition of Sodium Tetraphenylborate to (*E*)-3-Methyl-5-phenyl-2-pentenoates: Effect of Ester and Ligand



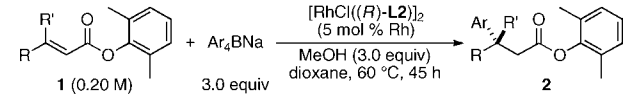
entry	substrate (R)	diene*	product	yield (%)[a]	ee (%)[b]
1	(*E*)-**1b** (Me)	cod	**2b**	60[c]	
2	(*E*)-**1b**	(*R*)-**L1**	**2b**	79	76
3	(*E*)-**1c** (*t*-Bu)	(*R*)-**L1**	**2c**	84	89
4	(*E*)-**1d** (2,6-$Me_2C_6H_3$)	(*R*)-**L1**	**2d**	93	97
5	(*E*)-**1d**	(*R*)-**L2**	**2d**	93	99
6	(*E*)-**1d**	(*R*,*R*)-Bn-bod*	**2d**	91	97
7	(*E*)-**1d**	(*R*,*R*)-Ph-bod*	**2d**	94	98

[a] Isolated yield. [b] Determined by chiral HPLC on a Chiralcel OD-H column with hexane/2-propanol = 100/1. [c] Determined by ^1H NMR of the crude material.



Under the conditions using $[RhCl((R)\text{-}\mathbf{L2})]_2$, the reaction of (*E*)-**1d** also proceeded well with only 1.0 equiv of sodium tetraphenylborate to give **2d** in acceptable yield of 79% with the same enantioselectivity (Table 2, entry 2). It is worth noting that the use of (*Z*)-**1d** as a substrate produced the opposite

Table 2. Rhodium-Catalyzed Asymmetric 1,4-Addition of Sodium Tetraarylborates to β,β-Disubstituted α,β-Unsaturated Esters **1**: Scope



entry	**1** (R, R′)	Ar	product	yield (%)[a]	ee (%)[b]
1	(*E*)-**1d** ($(CH_2)_2Ph$, Me)	Ph	(*S*)-**2d**	93	99
2[c]	(*E*)-**1d**	Ph	(*S*)-**2d**	79	99
3	(*Z*)-**1d** (Me, $(CH_2)_2Ph$)	Ph	(*R*)-**2d**	95	99
4[d]	(*E*)-**1e** ($(CH_2)_2Ph$, Et)	Ph	(*S*)-**2e**	90	99
5[d]	(*Z*)-**1e** (Et, $(CH_2)_2Ph$)	Ph	(*R*)-**2e**	89	99
6	(*E*)-**1f** ($(CH_2)_2CH{=}CMe_2$, Me)	Ph	(*S*)-**2f**	92[e]	97
7	(*E*)-**1g** (4-ClC_6H_4, Me)	Ph	(*S*)-**2g**	93	99
8	(*E*)-**1h** ($SiMe_2Ph$, Me)	Ph	(*S*)-**2h**	84	96
9[f]	(*E*)-**1d**	4-$MeOC_6H_4$	(*S*)-**2i**	90	98
10[f]	(*E*)-**1d**	4-MeC_6H_4	(*S*)-**2j**	89	98
11	(*E*)-**1d**	4-ClC_6H_4	(*S*)-**2k**	85	98
12[d,f]	(*E*)-**1d**	3-$MeOC_6H_4$	(*S*)-**2l**	64	96
13[f]	(*E*)-**1d**	3-MeC_6H_4	(*S*)-**2m**	96	98

[a] Isolated yield. [b] Determined by chiral HPLC with hexane/2-propanol. [c] The reaction was conducted using 1.0 equiv of Ph_4BNa and 1.0 equiv of MeOH at 0.40 M substrate concentration. [d] The reaction was conducted with 8 mol % of catalyst. [e] The product was obtained as a mixture of olefin isomers [(R = $(CH_2)_2CH{=}CMe_2$)/(R = $(CH_2)_3C(Me){=}CH_2$) = 93/7]. [f] The reaction was conducted in THF.

(8) Attempts to improve the yield of **2b** under the catalysis of $[RhCl(cod)]_2$ were not successful by further changing the stoichiometry, reaction temperature, etc.

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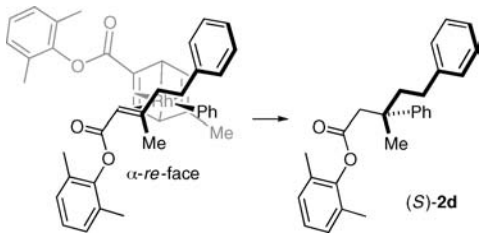
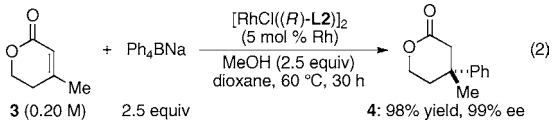


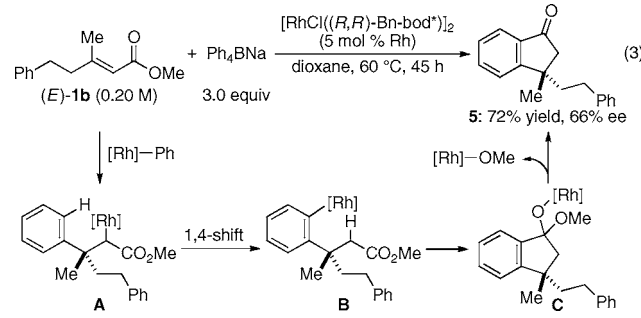
Figure 1. Proposed stereochemical pathway for the Rh/(*R*)-**L2**-catalyzed 1,4-addition of sodium tetraphenylborate to (*E*)-**1d**.

enantiomer of **2d** with 99% ee (entry 3), indicating that the catalyst efficiently recognizes the olefin geometry of the substrates. The same results were obtained for substrate **1e** having sterically very similar ethyl and 2-phenylethyl groups at the β-position (entries 4 and 5). In addition to alkyl groups, aryl and silyl groups are also tolerated at the β-position of substrates to give the corresponding 1,4-adducts in high yield with excellent enantioselectivity (entries 6−8). The present catalysis is not limited to these acyclic enoates and is applicable to cyclic substrates as well. For example, phenylation of α,β-unsaturated lactone **3** smoothly proceeds under similar conditions to give compound **4** in 98% yield with 99% ee (eq 2). With regard to the nucleophilic component, several other aryl groups can be effectively added to (*E*)-**1d** with uniformly high enantiomeric excesses (entries 9−13).



The stereochemical outcome in the reaction of (*E*)-**1d** with sodium tetraphenylborate under the catalysis of Rh/(*R*)-**L2** can be rationalized as shown in Figure 1. To minimize the unfavorable steric interaction between the ester group of (*E*)-**1d** and the substituent on the olefin of (*R*)-**L2**,[10] (*E*)-**1d** coordinates to phenylrhodium species with its α-*re* face, thereby leading to the formation of **2d** with *S* configuration.[15] This model can also well explain the formation of (*R*)-**2d** from (*Z*)-**1d** as demonstrated in Table 2, entry 3.

It is worth noting that the course of the present catalysis significantly changes by employing aprotic reaction conditions. For example, a reaction of (*E*)-**1b** with sodium tetraphenylborate in the absence of MeOH selectively gave 3,3-disubstituted 1-indanone **5** in 72% yield as shown in eq 3.[16,17] The formation of **5** rather than the simple 1,4-addition product (**2b**) can be explained as follows. Thus, insertion of the olefin of **1b** into a phenylrhodium species provides intermediate **A**. As a result of the aprotic reaction conditions, this intermediate does not undergo protonolysis, and instead, alkyl-to-aryl 1,4-rhodium migration preferentially takes place to give arylrhodium intermediate **B**.[18] Successive intramolecular insertion of ester carbonyl into this arylrhodium species,[19] followed by β-oxygen elimination from intermediate **C**, leads to the formation of indanone **5**.



In summary, we have developed a rhodium/diene-catalyzed 1,4-addition of sodium tetraarylborates to β,β-disubstituted α,β-unsaturated esters. Highly efficient asymmetric catalysis has also been described to create quaternary carbon stereocenters at the β-position of esters by tuning the ester group of substrates and employing chiral diene (*R*)-**L2** as the ligand. In addition, a new way of constructing 3,3-disubstituted 1-indanones has also been discovered by conducting the arylation reactions under aprotic conditions.

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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) See Supporting Information for the assignment of the absolute configuration.

(16) (a) Almost no reaction took place with 2,6-dimethylphenyl ester (*E*)-**1d**. (b) The use of other chiral diene ligands resulted in lower yield and ee (e.g., (*R*)-**L1**: 31% yield, 61% ee. (*R*)-**L2**: 33% yield, 60% ee. (*R,R*)-Ph-bod*: 61% yield, 60% ee). (c) When the reaction of (*E*)-**1b** was conducted using Rh/(*R,R*)-Bn-bod* catalyst in the presence of MeOH, 1,4-adduct **2b** was obtained in 62% yield with 75% ee. Somewhat lower ee value of **5** in eq 3 is probably due to the partial isomerization of substrate (*E*)-**1b** to (*Z*)-**1b** under the reaction conditions, which was confirmed in the remaining **1b** after the reaction.

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