Tetrahedron Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Rhodium catalyzed asymmetric 1,4-addition of arylboronic acids to β,γ-unsaturated α-keto ester using chiral *tert*-butanesulfinylphosphines ligands

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ARTICLE INFO

Article history:
Received 18 March 2014
Revised 16 April 2014
Accepted 22 April 2014
Available online xxxx

Keywords:
Rh-Catalyzed
β,γ-Unsaturated α-keto ester
1,4-Selective addition
Asymmetric catalysis
tert-Butanesulfinylphosphine

ABSTRACT

Rh-Catalyzed asymmetric 1,4-selective addition of arylboronic acids to β,γ-unsaturated α-keto ester was developed using chiral *tert*-butanesulfinylphosphine as ligand, good yields (up to 87%), good 1,4-regioselectivities (up to 96:4), and high enantioselectivities (up to 94% ee) were achieved.

Since developed by Hayashi and miyaura, Rh-catalyzed asymmetric conjugated addition (ACA) of arylboronic acids to electron-deficient olefins has become an important strategy for enantioselective carbon–carbon bond formation.[1] During the past decade, a broad scope of electron-deficient substrates, such as α,β-unsaturated aldhyde,[2] ketones,[1a,3] esters,[4] amides,[5] sulfones,[6] phosphonates,[7] nitro alkenes[8] and so on, have been extensively exploited. Albeit β,γ-unsaturated α-ketoesters have been widely applied in many reactions owing to their dense functionalizations,[9] it is still a class of challenging substrates for Rh-catalyzed ACA. In 2008, Zhou et al. realized an 1,2-addition of arylboronic acid to β,γ-unsaturate α-ketoesters by using a Rh/spirophosphite catalytic system, moderate to excellent yield (up to 93%) and excellent enantionselectivity (up to 93%) were achieved.[10] Very recently, by using sulfinamide–olefin ligand, Xu et al. reported an example of 1,4-adduct as the major product for the Rh-catalyzed 1,2-/1,4-selective addition of arylboronic acid to β,γ-unsaturated α-ketoester, however, only 5% ee for 1,4-adduct was observed.[11] Our recent interest was focused on designing chiral sulfoxide ligands and developing their application in asymmetric transition-metal catalyzed reactions.[12] In this work, we would like to present a rhodium catalyzed asymmetric 1,4-selective addition of arylboronic acids to β,γ-unsaturated α-ketoester by using *tert*-butanesulfinylphosphine as ligand.

The initial reaction was carried out with ethyl 2-oxo-4-phenylbutyrate (**1a**), 2 equiv of $PhB(OH)_2$ (**2a**), and 50 mol % KOH (1.0 M in H_2O) in the presence of (1.0 mol %) $[Rh(CH_2CH_2)_2Cl]_2$/(3 mol %)sulfinylphosphine **L1**. The reaction proceeded smoothly in dichloromethane (DCM) at 40 °C for 4 h, to our delight, the 1,4-adduct was obtained as major product and with good isolated yield and modest enantioselectivity (73% yield and 60% ee, Table 1, entry 1). Encouraged by this result, we next systematically screen the reaction condition. The solvent dramatically affected the 1,4/1,2-selectivity and alcohols were proved to be the best solvent for the regioselectivity (Table 1, entries 2–5). Although ethyl alcohol can provide up to 95:5 ratio of 1,4/1,2-adduct, the yield was poor due to the hydrolysis of substrate and product under the strong basic condition (Table 1, entry 4). Trifluoroethanol (CF_3CH_2OH) was identified as ideal solvent to give the 1,4-adduct in good yield with moderate enantiomeric excess (86% yield and 52% ee, Table 1, entry 5). In addition, the excellent regioselectivity was obtained in the presence of KOH (Table 1, entries 5–8). $[Rh(COD)Cl]_2$ was used and the result did not have great change. (Table 1, entry 9). We then evaluated different ligands in the optimized conditions, bifunctional sulfinylphosphine ligand (**L9**),[13] bissulfoxide (**L10**),[12d] sulfoxide-olefin (**L11**),[12j] and (*R*)-BINAP (**L12**) demonstrated no reactivity. Other sulfinylphosphines

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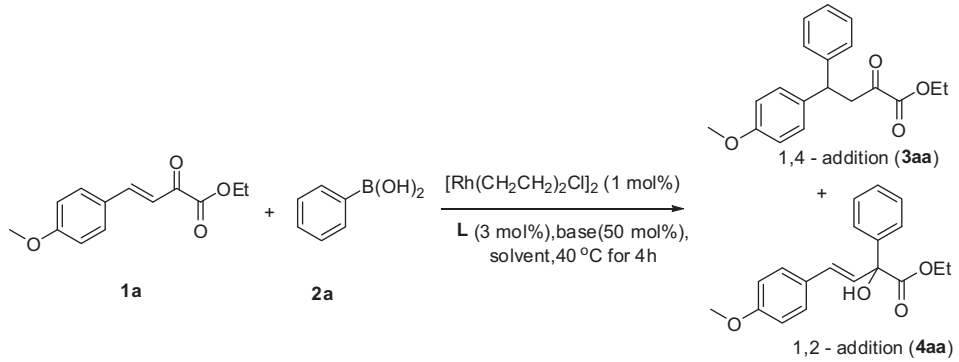
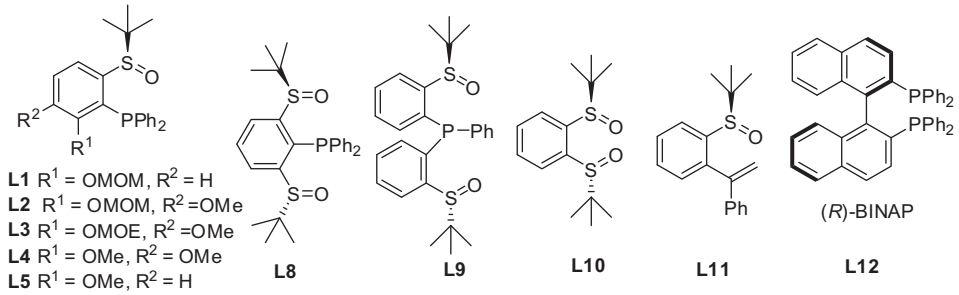
http://dx.doi.org/10.1016/j.tetlet.2014.04.074
0040-4039/

Table 1
Reaction conditions screening



Ligands:



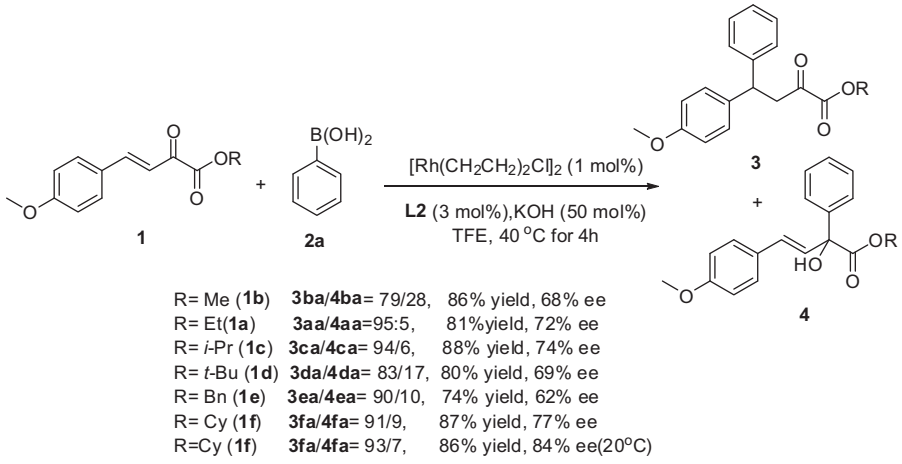
Entry	Ligand	Solvent	Base	1,4-/1,2-adduct[b]	Yield (**3aa**)[c] (%)	ee (**3aa**)[d] (%)
1	**L1**	DCM	KOH	84:16	73	60
2	**L1**	DCE	KOH	82:18	69	53
3	**L1**	THF	KOH	86:14	53	49
4	**L1**	EtOH	KOH	95:5	46	62
5	**L1**	CF_3CH_2OH	KOH	92:8	86	52
6	**L1**	CF_3CH_2OH	K_2CO_3	71:29	56	66
7	**L1**	CF_3CH_2OH	Cs_2CO_3	83:17	53	64
8	**L1**	CF_3CH_2OH	^tBuOK	85:15	68	60
9[e]	**L1**	CF_3CH_2OH	KOH	86:14	65	56
10	**L2**	CF_3CH_2OH	KOH	95:5	81	72
11	**L3**	CF_3CH_2OH	KOH	91:9	88	70
12	**L4**	CF_3CH_2OH	KOH	92:8	80	64
13	**L5**	CF_3CH_2OH	KOH	93:7	72	57
14	**L6**	CF_3CH_2OH	KOH	93:7	80	50
15	**L7**	CF_3CH_2OH	KOH	96:4	83	55
16	**L8**	CF_3CH_2OH	KOH	75:25	47	76
17	**L9**	CF_3CH_2OH	KOH	nd	nr	nd
18	**L10**	CF_3CH_2OH	KOH	nd	Trace	nd
19	**L11**	CF_3CH_2OH	KOH	nd	Trace	nd
20	**L12**	CF_3CH_2OH	KOH	nd	nr	nd

[a] Reaction conditions: 0.3 mmol of **1a**, 2.0 equiv of **2a**, 1 mol % of $[Rh(CH_2CH_2)_2Cl]_2$, 3 mol % of ligand, 0.5 equiv of base (1.0 M in H_2O) in 1 mL of solvent at 40 °C for 4 h.
[b] Determined by ^1H NMR of the crude product.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.
[e] $[Rh(COD)Cl]_2$ was used. nr = no reaction, nd = no determined.

(**L2**–**L7**) and bissulfinylphosphine (**L8**)[14] could also promote this reaction (Table 1, entries 10–16) and **L2** was the best ligand (81% yield and 72% ee). The electron-donating substituted (**L2**–**L4**) groups are good for the enantioselectivity.

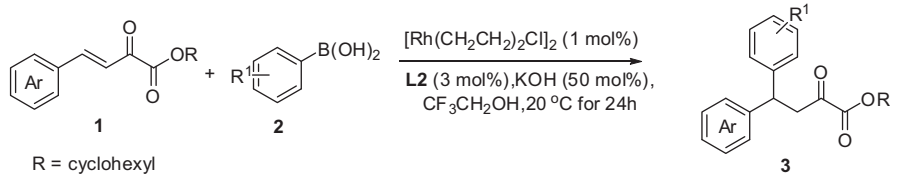
Finally, we examined effects of the ester group for substrate **1** on the reactivity, regioselectivity and enantioselectivity of the reaction.[9j] Several esters, such as methyl-**1b**, isopropyl-**1c**, *tert*-butyl-**1d**, benzyl-**1e**, and cyclohexyl-**1f** were evaluated and the results are summarized in Scheme 1. Isopropyl-**1c** and cyclohexyl-**1f**, afforded both good regioselectivity and enantioselectivity. The reaction (for substrate **1f**) proceeded smoothly at 20 °C and 1,4-adduct **3fa** was obtained with high regioselectivity (93:7), high enantioselectivity (84% ee), and high yield (86%).

With optimal condition in hand,[15] we investigated the scope of β,γ-unsaturated α-keto esters and arylboronic acids (Table 2). A variety of β,γ-unsaturated α-keto esters were subjected to the reaction with phenylboronic acid **2a** and gave the desired 1,4-addition products **3fa–3qa** in good yields (70–87%) and with moderate to good ee values (60–84%). Electron-rich groups of *para*-substituents afforded better enantioselectivity than electron-poor ones and the steric hindrance showed little influence on the reactivity, regioselectivity and enantioselectivity (Table 2, entries 1–7). 3,4-Dichlorosubstituted **1m**, *meta*-chloro/fluoro-substituted **1n** or **1o** reacted with phenylboronic acid **2a** to afford the corresponding products **3ma**, **3na**, and **3oa** with good results (Table 2, entries 8–10). *ortho*-Chlorosubstituted **1p** also proceeded smoothly



Scheme 1. Screening ester group of substrates.

Table 2
Substrate scope of asymmetric 1,4-addition to (*E*)-2-oxo-4-arylbut-3-enoate



Entry	Ar (**1**)	R^1 (**2**)	1,4-/1,2-adduct[b]	Yield (**3**)[c] (%)	ee (**3**)[d] (%)
1	*p*-$MeOC_6H_4$ (**1f**)	H (**2a**)	93:7	86	84 (**3fa**)
2	*p*-^{i}prC_6H_4 (**1g**)	H (**2a**)	94:6	87	83 (**3ga**)
3	*p*-^{t}Bu C_6H_4 (**1h**)	H (**2a**)	96:4	86	84 (**3ha**)
4	*p*-MeC_6H_4 (**1i**)	H (**2a**)	94:6	81	80 (**3ia**)
5	*p*-FC_6H_4 (**1j**)	H (**2a**)	92:8	83	77 (**3ja**)
6[e]	*p*-Cl C_6H_4 (**1k**)	H (**2a**)	91:9	79	73 (**3ka**)
7[e]	*p*-CN C_6H_4 (**1l**)	H (**2a**)	90:10	70	60 (**3la**)
8	3,4-Cl C_6H_4 (**1m**)	H (**2a**)	92:8	82	60 (**3ma**)
9	*m*-Cl C_6H_4 (**1n**)	H (**2a**)	94:6	85	74 (**3na**)
10	*m*-F C_6H_4 (**1o**)	H (**2a**)	92:8	78	77 (**3oa**)
11	*o*-Cl C_6H_4 (**1p**)	H (**2a**)	86:14	77	71 (**3pa**)
12	2-thiophenyl (**1q**)	H (**2a**)	85:15	75	64 (**3qa**)
13	C_6H_5 (**1r**)	*p*-MeO (**2b**)	81:19	75	71 (**3rb**)
14	*p*-$MeOC_6H_4$ (**1f**)	*p*-^{t}Bu (**2c**)	85:15	73	92 (**3fc**)
15	*p*-$MeOC_6H_4$ (**1f**)	*p*-^{i}pr (**2d**)	86:14	72	94 (**3fd**)
16	*p*-$MeOC_6H_4$ (**1f**)	*p*-OTBS (**2e**)	77:23	66	88 (**3fe**)
17	*p*-$MeOC_6H_4$ (**1f**)	*p*-OBn (**2f**)	81:19	74	80 (**3ff**)
18	*p*-$MeOC_6H_4$ (**1f**)	*p*-Me (**2g**)	87:13	78	80 (**3fg**)
19	*p*-$MeOC_6H_4$ (**1f**)	*p*-OMOM (**2h**)	80:20	67	77 (**3fh**)
20	*p*-$MeOC_6H_4$ (**1f**)	*p*-CF_3 (**2i**)	91:9	72	54 (**3fi**)
21	*p*-$MeOC_6H_4$ (**1f**)	*m*-OMe (**2j**)	92:8	87	71 (**3fj**)
22	*p*-$MeOC_6H_4$ (**1f**)	*m*-Cl (**2k**)	88:12	71	74 (**3fk**)
23	*p*-$MeOC_6H_4$ (**1f**)	*m*-Naphthyl (**2l**)	83:17	64	69 (**3fl**)

[a] Reaction conditions: 0.3 mmol of (*E*)-2-oxo-4-arylbut-3-enoate **1**, 2.0 equiv of arylboronic acid **2**, 1 mol % of $[Rh(CH_2CH_2)_2Cl]_2$, 3 mol % of **L2**, 0.5 equiv of KOH (1.0 M in H_2O) in 1 mL of CF_3CH_2OH at 20 °C for 24 h.
[b] Determined by ^{1}H NMR of the crude product.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.
[e] At 40 °C for 4 h.

(Table 2, entry 11). Heterocyclic, like thiophenyl, substrate **1q** also worked well with **2a** to give **3qa** in good yield (75%) and moderate ee value (64%).

In the examination of arylboronic acids scope, we found that stereoelectronic properties of aryl groups have great influence on the outcome of the reaction. Electron-rich substituents were benefited to the enantioselectivity (Table 2, entries 14–18). For instance, (*p*-^{t}Bu)phenyl and (*p*-*i*-propyl)phenyl boronic acids provided adducts **3fc** and **3fd** with excellent enantiomerical excess (92% and 94%). The type of *m*-substituents on arylboronic acids have little effect on the reaction, (Table 2, entries 21–23) but *o*-substituted arylboronic acids showed no reactivity, probably due to the huge steric hindrance.

In summary, we developed a Rh-catalyzed asymmetric 1,4-selective addition of arylboronic acids to β,γ-unsaturated α-keto ester using *tert*-butanesulfinylphosphines as ligand, moderate to excellent 1,4-regioselectivities (up to 96:4), good yields (up to 87%), and good enantioselectivities (up to 94% ee) were achieved.

Please cite this article in press as: Wang, J.; et al. *Tetrahedron Lett.* (2014), http://dx.doi.org/10.1016/j.tetlet.2014.04.074

Detailed mechanism study on 1,4-/1,2-selectivity and enantioselectivity of this reaction is in progress.[16]

Acknowledgments

We are grateful to the support of National Science Foundation of China (21272226 and 21202160) and the Major State Basic Research Development Program (973 program, 2010CB833300).

Supplementary data

Supplementary data (experiment details, copies of HPLC, ^{1}H and ^{13}C NMR spectra for products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.074.

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15. *Procedure for rhodium catalyzed asymmetric selectivity 1,4-addition of arylboronic acids to β, γ-unsaturated α-keto ester:* Under an argon atmosphere and at room temperature, to a 10 mL Schlenk tube with a teflon cap was added ligand **L2** (5.5 mg. 3 mol %) and $[Rh(C_2H_4)_2Cl]_2$ (1.2 mg, 1 mol %) followed by 1.0 mL DCM. The mixture was stirred for half hour, after removal of the solvent, (*E*)-2-oxo-4-arylbut-3-enoate (0.3 mmol), arylboronic acid (0.6 mmol) and degassed KOH (1.0 M in H_2O, 0.15 mL, 0.15 mmol). The reaction mixture was stirred at 20 °C for 24 h. The reaction mixture was then directly charged on to a column (silica gel) for flash chromatography with a mixture of petroleum ether/EtOAc (15:1) to afford the product.
16. A proposed 1,4-/1,2-selective addition model was provided in Supporting information.