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Synthesis of Quaternary Carbon-containing β^{2,2}-Amino Acids via Rh(I)-Catalyzed Enantioselective Arylation of α-Substituted β-Nitroacrylates

Jo-Hsuan Fang, Jia-Hong Jian, Hao-Ching Chang, Ting-Shen Kuo, Way-Zen Lee, Ping-Yu Wu and Hsyueh-Liang Wu*[a]

Dedication ((optional))

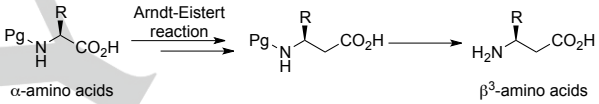
Abstract: An enantioselective Rh(I)-catalyzed conjugate addition reaction of α-substituted β-nitroacrylates with various arylboronic acids using Rh(I)-chiral diene catalysts is described for the first time. The addition reaction proceeds under mild conditions in a range of common organic solvents and additives offers the corresponding quaternary carbon-containing α,α-disubstituted β-nitropropionate products in up to 63% yield with up to 99% ee. Reaction of (*E*)- or (*Z*)-β-nitroacrylates both provide the same enantiomer, and a range of esters and aryl groups are tolerated. To demonstrate the utility of the method ethyl (*R*)-1,1-methyl-1-phenyl-3-nitropropionate, prepared herein, was converted to the non-proteinogenic β^{2,2}-amino acid, (*R*)-2-(aminomethyl)-2-phenylpropanoic acid, and to the β^{2,2}-lactam, (*R*)-3-methyl-3-phenylazetidin-2-one. In addition, a tripeptide comprising L-phenylalanine, L-alanine, and β^{2,2}-amino acid **7** was also synthesized.

Introduction

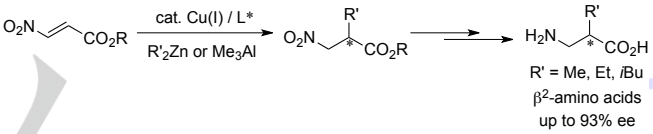
β-Amino acids and their derivatives have attracted considerable synthetic interest owing to their ubiquity in natural products[1] and pharmaceuticals as well as their importance as structural motifs in β-peptides[2a,b] and β-lactams.[2c,d] While one carbon homologation of natural amino acids via the Arndt–Eistert reaction provides facile access to β^3-amino acids (β-substituted-β-amino acids; Scheme 1a),[3] asymmetric synthesis of their β^2-congeners (α-substituted β-amino acids) is comparably challenging, prompting considerable synthetic endeavors toward their preparation.[3,4] The catalytic asymmetric addition reaction of nucleophiles to β-nitroacrylates followed by reduction of the nascent α-substituted β-nitroacrylates and hydrolysis provides convenient access to β^2-amino acids. Examples of this include the Cu(I)-catalyzed conjugate addition of Et_2Zn[4a,b] and Me_3Al[4c,e] to β-nitroacrylates (Scheme 1b) and the Pd(II)-catalyzed arylation of β-nitroacrylamides[4h] using arylboronic acids (Scheme 1c). In addition, enzymatic[4d] and organocatalytic[4g] transfer hydrogenation of α-substituted β-nitroacrylates (Scheme 1d) have been used to generate optically active β^2-amino acids with ees of up to 96%. More interestingly and of relevance to our own work, however, the asymmetric addition of nucleophiles to α-substituted β-nitroacrylates has enabled the synthesis of enantioenriched β^{2,2}-amino acids that harbor chiral quaternary carbon centers (Scheme 1e).[5]

Scheme 1.

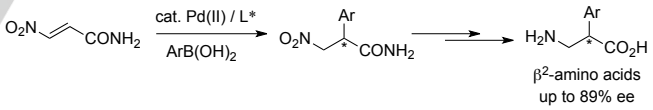
(a) Synthesis of β^3-amino acids using the Arndt-Eistert reaction of α-amino acids



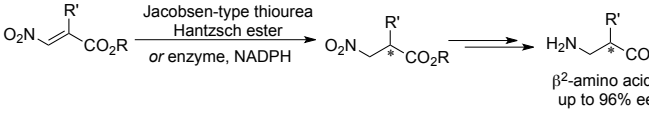
(b) Cu(I)-catalyzed addition of diorganozincs and Me_3Al to β-nitroacrylates



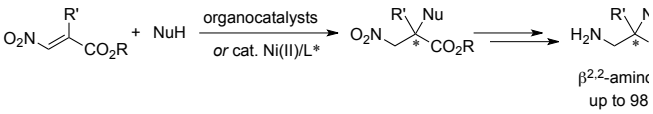
(c) Pd(II)-catalyzed addition of arylboronic acids to β-nitroacrylamide



(d) Asymmetric reduction of α-substituted β-nitroacrylates



(e) Asymmetric addition of α-substituted β-nitroacrylates



In recent years, Rh(I)-catalyzed conjugate addition reactions have been proven capable of delivering high enantioselectivities in a variety of C-C bond forming processes, while exhibiting good catalytic activity in the presence of a variety of common functional groups and in aqueous reaction media.[6] In addition to a variety of additions reactions,[7] we recently reported[7d] the efficient and enantioselective 1,4-conjugate addition reaction of arylboronic acids to β-nitroolefins, exploiting Rh(I)-catalysts bearing novel chiral 2,5-diarylbicyclo[2.2.1]heptadiene ligands.[7k] In fact, the screening of a library of these ligands revealed that

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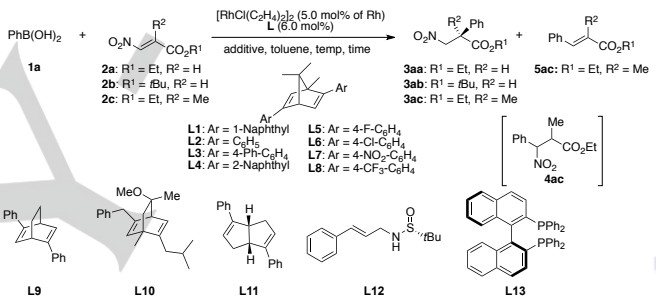
the 2,5-di-naphth-1-yl substituted ligand provided the highest enantioselectivity for a model substrate. While disclosures from other groups[8] have demonstrated additions to nitroolefins, dienes[9] have proven useful as Rh(I) ligands. As a logical extension of our prior variant[7d] of the Hayashi−Miyaura reaction using nitroolefins as Michael acceptors, we herein present for the first time the Rh(I)-catalyzed enantioselective conjugate addition of arylboronic acids to α-substituted β-nitroacrylates offering α,α-disubstituted β-nitropropionates that contain quaternary carbon centers. These compounds are useful en routé to β[2,2]-amino acids and their derivatives.

Results and Discussion

The current study began by examining the conjugate addition of phenylboronic acid (**1a**) to ethyl (**2a**) and *tert*-butyl (**2b**) (*E*)-nitroacrylates, employing the previously identified[7d] conditions found optimal for the corresponding addition reaction of β-nitroolefins. Disconcertingly, however, reactions carried out in the presence of 0.5–5 mol% of the Rh(I)/**L1** catalyst using KHF_2 as an additive failed to yield the desired products **3aa** or **3ab** (Table 1, entries 1 and 2). When KOH was used instead of KHF_2, the desired products **3aa** or **3ab** were obtained, albeit in low yields (23% and 31%) with only moderate enantioselectivities (79% and 83% ee) (entries 3 and 4). This suggested that β-nitroacrylates were more challenging substrates than the corresponding β-nitroolefines. While frustrated by the results obtained when applying our proprietary[7j] set of chiral 2,5-diarylbicyclo[2.2.1]heptadiene ligands (**L2**–**L8**) to the reaction of **2a** and **2b**,[10] when the addition reaction was tested on the α-substituted nitroacrylate **2c** instead, the corresponding addition product **3ac** was produced in 42% yield with 97% ee (entry 5). A substantial amount of the reaction mass balance was accounted for by the formation of styrene **5ac**; isolated in 32% yield. In fact, ^{1}H NMR spectroscopic analysis of the crude product mixture revealed that **3ac** and **5ac** were formed in a 1.2:1 ratio indicating that the conjugate addition had proceeded with only slight regioselectively. To explain the formation of **5ac**, it is probable that ethyl 2-methyl-3-nitro-3-phenylpropionate (**4ac**) was produced as a transient intermediate that then underwent elimination of nitrous acid.[11] The yield, regioselectivity and ee were slightly improved when the reaction of **2c** was performed at 40 °C (entry 6), but reducing the catalyst loading to 3 mol% of Rh(I) resulted in a significant decrease in reaction rate and a small decrease in the ee (entry 7). Conducting the reaction at room temperature garnered no improvement (entry 8).

Having previously found that Rh(I)-catalyzed 1,2- and 1,4-addition reactions each require different ligands for optimum ees for each specific substrate class, we next screened our library[7j] of 2,5-substituted chiral bicyclo[2.2.1]heptadiene ligands (entries 9–15) using the conditions of entry 6 (toluene, 40 °C, 3 h). In all cases the ees and yields were lower than that of entry 6, despite the regioselectivity being significantly improved (**3ac**/**5ac** ratio was 4.7:1 and 4.5:1) when using the di-(4-fluorophenyl)- and di-(4-trifluoromethylphenyl)- ligands **L5** and **L8** (entries 12 and 15), respectively. Poignantly, entries 9–12 and 14–15 show that higher conjugate addition regioselectivity occurs at the expense of ee. Amidst the chiral diene ligands tested, none provided better ee or yields than the 1-naphthyl substituted chiral diene **L1** (entry 6); it is notable that this ligand proved best for the corresponding 1,4-conjugate additions to β-nitroolefins.[7d] In addition our ligands examined above, a number of related available ligands (**L9**–**L13**) that have been shown elsewhere to provide good reactivity and enantioselectivity in asymmetric Rh-catalyzed arylations of α,β-unsaturated carbonyl compounds were tested. While the desired adduct **3ac** was obtained in 53% in the presence of Rh-catalyst comprising our diene ligand **L1** (entry 6), dienes **L9**,[12a] **L10**,[12b] or **L11**[12c] all failed to provide any of the desired product within 24 h under identical reaction conditions as identified in entry 6 (entries 16–18). Similarly, carrying out the arylation of **2c** using sulfinamide-olefin hybrid ligand **L12**[12d] or (*S*)-BINAP (**L13**)[12e] afforded none of the desired addition product **3ac** (entries 19 and 20).

Table 1. Conjugate addition of phenylboronic acid (**1a**) to β-nitroacrylates **2**[a]



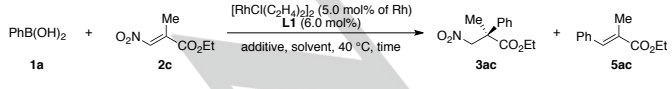
Entry	2	L	Additive	t (°C)	Time (h)	3ac/ 5ac[b]	Yield (%)[c]	ee (%)[d]
1	**2a**	**L1**	KHF_2	50	24	N.D.	N.R.	N.D.
2	**2b**	**L1**	KHF_2	50	24	N.D.	N.R.	N.D.
3	**2a**	**L1**	KOH	50	24	N.D.	23 (**3aa**)	79
4	**2b**	**L1**	KOH	50	24	N.D.	31 (**3ab**)	83
5[e]	**2c**	**L1**	KHF_2	50	3	1.2	42 (**3ac**)	97
6	**2c**	**L1**	KHF_2	40	3	1.3	53 (**3ac**)	99
7[f]	**2c**	**L1**	KHF_2	40	12	1.5	42 (**3ac**)	96
8	**2c**	**L1**	KHF_2	24	18	1.0	36 (**3ac**)	98
9	**2c**	**L2**	KHF_2	40	24	3.2	12 (**3ac**)	51
10	**2c**	**L3**	KHF_2	40	24	3.8	14 (**3ac**)	44
11	**2c**	**L4**	KHF_2	40	24	3.7	18	62

							(**3ac**)	
12	**2c**	**L5**	KHF_2	40	24	4.7	25 (**3ac**)	48
13	**2c**	**L6**	KHF_2	40	24	1.4	40 (**3ac**)	84
14	**2c**	**L7**	KHF_2	40	24	3.8	12 (**3ac**)	54
15	**2c**	**L8**	KHF_2	40	24	4.5	25 (**3ac**)	56
16	**2c**	**L9**	KHF_2	40	24	N.D.	N.R.	N.D.
17	**2c**	**L10**	KHF_2	40	24	N.D.	N.R.	N.D.
18	**2c**	**L11**	KHF_2	40	24	N.D.	N.R.	N.D.
19	**2c**	**L12**	KHF_2	40	24	N.D.	N.R.	N.D.
20	**2c**	**L13**	KHF_2	40	24	N.D.	N.R.	N.D.

[a] Conducted in toluene (0.8 mL) using β-nitroacrylate **2c** (0.2 mmol), boronic acid **1a** (0.6 mmol, 3.0 equiv based on **2c**) and KHF_2 (3.0 M, 0.4 mL, 1.2 mmol) in the presence of Rh(I) catalyst prepared in situ from $[RhCl(C_2H_4)_2]_2$ (5.0 μmol, 5.0 mol% of Rh) and chiral diene **L1** (12 μmol, 6.0 mol%); reactions were worked up when TLC indicated completion, or at 24 h, whichever came first. N.D. = not determined. N.R. = no reaction; recovered starting material. [b] Ratios determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Isolated yield. [d] Determined by HPLC analysis using chiral columns. [e] A 32% yield of **5ac** was isolated. [f] Rh(I) catalyst prepared in situ from $[RhCl(C_2H_4)_2]_2$ (3.0 μmol, 3.0 mol% of Rh) and chiral diene **L1** (7.2 μmol, 3.6 mol%).

Using the general conditions specified in Table 1, entry 6, a screen of base additives and solvents was conducted next using phenylboronic acid (**1a**) and (*E*)-2-methyl-3-nitroacrylate (**2c**). While the majority of the common bases tested afforded comparable yields of **3ac** (44–47%) and ees (94–95%), $NaHCO_3$ (entry 3) and KOH (entry 8) provided moderately improved yields of 56% and 55%, respectively (Table 2, entries 1–8). While amines bases have proven optimal in some addition reactions of boronic acids to Michael acceptors,[7a,7f,7g] no reaction was observed when Et_3N was employed in the present study (entry 9). In terms of ee, however, no base additive provided better results than was achieved with KHF_2 (Table 1, entry 6), and therefore this was used in subsequent tests. While the reaction performed effectively in a variety of solvents with ees of 95–97% (entries 10–17), yields of **3ac** were inferior to that achieved in toluene (Table 1, entry 6). Notably, carrying out the reaction in MeOH or *i*PrOH in the presence of KHF_2 produced no transesterification products (entries 15 and 17).

Table 2. Additive and solvent screening[a]



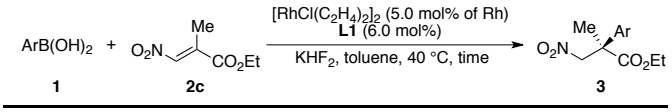
Entry	Additive	Solvent	Time (h)	**3ac**/**5ac**[b]	**3ac** (%)[c]	ee (%)[d]
1	LiOH	toluene	5	1.3	47	95
2	NaOH	toluene	7	1.4	44	95
3	$NaHCO_3$	toluene	5	1.4	56	96
4	*t*BuOK	toluene	4	1.3	45	94
5	K_2CO_3	toluene	4	1.2	47	94
6	K_3PO_4	toluene	5	1.4	44	95
7	KF	toluene	5	1.2	46	95
8	KOH	toluene	3	1.4	55	94
9	Et_3N	toluene	3	N.D.[e]	N.R.[f]	N.D.[e]
10	KHF_2	xylene	3	1.4	45	96
11	KHF_2	THF	3	0.9	28	96
12	KHF_2	dioxane	3	1.0	38	96
13	KHF_2	Et_2O	3	0.9	22	97
14	KHF_2	CH_2Cl_2	3	1.5	39	95
15	KHF_2	MeOH	3	1.6	37	95
16	KHF_2	EtOH	3	1.4	37	95
17	KHF_2	*i*PrOH	3	1.3	41	96

[a] The reaction was conducted in toluene (0.8 mL), unless otherwise stated, using β-nitroacrylate **2c** (0.2 mmol), boronic acid **1a** (0.6 mmol, 3.0 equiv based on **2c**) and KHF_2 (3.0 M, 0.4 mL, 1.2 mmol), in the presence of rhodium catalyst prepared in situ from $[RhCl(C_2H_4)_2]_2$ (5.0 μmol, 5.0 mol% of Rh) and chiral diene **L1** (12 μmol, 6.0 mol%); reactions were monitored by TLC. Variation: other additives (1.0 M, 0.4 mL) or solvents were used. [b] Ratios determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. [c] Isolated yield. [d] Determined by HPLC analysis using a chiral AS-H column. [e] N.D. = not determined. [f] N.R. = no reaction; recovered starting material.

Using the preferred conditions (Table 1, entry 6), the asymmetric addition of a variety of electron rich and electron poor arylboronic acids **1** to β-nitroacrylate **2c** was examined next (Table 3). While the reactions of 3-tolyl- and 4-tolylboronic acids (**1b** and **1c**) gave addition products **3bc** and **3cc** in 50 and 47% yield, respectively, with high stereoselectivities (entries 1 and 2), no reaction was observed when the conjugate addition of 2-tolylboronic acid (**1d**) (entry 4) was attempted, presumably a result of the bulky *ortho* substituent. The chemical yield of **3cc** was slightly higher when the reaction of **2c** and 4-tolylboronic acid (**1c**) was conducted in the presence of $NaHCO_3$ (entry 3) instead of KHF_2. Arylboronic acids bearing electron releasing groups at their 3- or 4-positions were good reaction partners (entries 5–8), providing addition products **3ec**–**3hc** in 45–63% yield with 94–97% ee. While the asymmetric addition of sterically encumbered 1-naphthylboronic acid (**1i**) proceeded very inefficiently (entry 9), reaction of its isomer, 2-naphthylboronic acid (**1j**), afforded **3jc** in a relatively pleasing 51% yield with 95% ee (entry 10). Arylboronic acids possessing electron withdrawing groups were examined next (entries 11–17). While 4-fluorophenylboronic acid (**1k**) afforded a satisfying 59% yield of **3kc** with 94% ee (entry 11), 4-chloro- (**1l**), 3,4-dichloro- (**1m**), 3-NO_2- (**1n**), 3-CF_3- (**1o**) and 4-CF_3-phenylboronic acid (**1p**) all proceeded slowly giving low 7–24% yields (18–49% yield based on recovered starting material) of addition products **3lc**–**3pc**

after 24 hours of reaction (entries 12–17). Despite this, good to high enantioselectivities (87–95% ee) were witnessed for these substrates. Moreover, conducting the asymmetric addition reaction employing (*E*)-styrylboronic acid (**1q**) furnished the corresponding adduct **3qc** in 20% yield and with diminished stereoselectivity (75% ee) (entry 18).

Table 3. Asymmetric addition of arylboronic acids **1** to β-nitroacrylate **2c**[a]



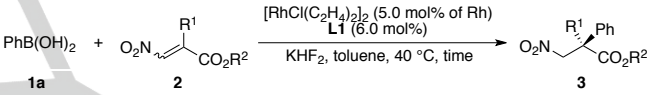
1 **2c** **3**

Entry	Ar	Time (h)	**3** (%)[b]	ee (%)[c]
1[d]	3-Me-C_6H_4 (**1b**)	24	50 (**3bc**)	96
2	4-Me-C_6H_4 (**1c**)	3	47 (**3cc**)	97
3[e]	4-Me-C_6H_4 (**1c**)	3	53 (**3cc**)	97
4	2-Me-C_6H_4 (**1d**)	24	N.R.	N.D.
5[d]	4-*t*Bu-C_6H_4 (**1e**)	24	63 (**3ec**)	97
6[d]	4-Ph-C_6H_4 (**1f**)	16	48 (**3fc**)	94
7[d]	3-MeO-C_6H_4 (**1g**)	16	47 (**3gc**)	96
8[d]	4-MeO-C_6H_4 (**1h**)	16	45 (**3hc**)	95
9[d]	1-Naphthyl (**1i**)	24	7 (11)[f] (**3ic**)	72
10	2-Naphthyl (**1j**)	3	51 (**3jc**)	95
11[d]	4-F-C_6H_4 (**1k**)	24	59 (**3kc**)	94
12[d]	4-Cl-C_6H_4 (**1l**)	24	24 (49)[f] (**3lc**)	93
13[d]	3,4-Cl_2-C_6H_3 (**1m**)	24	7 (38)[f] (**3mc**)	93
14	3-NO_2-C_6H_4 (**1n**)	12	12 (21)[f] (**3nc**)	87
15[d]	3-CF_3-C_6H_4 (**1o**)	24	18 (49)[f] (**3oc**)	95
16[d]	4-CF_3-C_6H_4 (**1p**)	24	13 (18)[f] (**3pc**)	92
17[e]	4-CF_3-C_6H_4 (**1p**)	24	15 (31)[f] (**3pc**)	92
18[d]	C_6H_5CH=CH (**1q**)	24	20 (39)[f] (**3qc**)	75

[a] Conducted in toluene (0.8 mL) using β-nitroacrylate **2c** (0.2 mmol), boronic acids **1** (0.6 mmol, 3.0 equiv based on **2c**) and KHF_2 (3.0 M, 0.4 mL, 1.2 mmol) in the presence of rhodium catalyst prepared in situ from $[RhCl(C_2H_4)_2]_2$ (5.0 μmol, 5.0 mol% of Rh) and chiral diene **L1** (12 μmol, 6.0 mol%); reactions were worked up when TLC indicated completion, or at 24 h, whichever came first; ratios of regioisomers **3**/**5** ranged 0.3–1.7, as determined by ^{1}H NMR spectroscopic analysis of crude mixtures. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Additional KHF_2 (3.0 M, 0.4 mL) was added after 12 h. [e] $NaHCO_3$ (1.0 M, 0.4 mL, 0.4 mmol) was used as an additive. [f] Yield based on recovered **2c**.

Having shown that a variety of aryl substituents could be stereoselectively incorporated into the α-position of 1-methyl-3-nitropropionates **3** by conjugate addition (Table 3), we next examined the variation of the other α-substituent using phenylboronic acid (**1a**) as the nucleophile donor (Table 4). The influences of the ester group and double bond geometry were also investigated. Keeping the α-substituent fixed as methyl, addition to esters **2d**–**2h** afforded the desired nitropropionates **3ad**–**3ah** in 20–41% yields with 99% ee in all cases (entries 1–5). A substantial decrease in stereoselectivity was observed when the α-substituent of nitroacrylates **2** was changed to ethyl ((*E*)-**2i** and (*E*)-**2j**) with the corresponding addition products produced in 33% and 23% yield with 84% and 73% ee, respectively (entries 6 and 7). Again fixing the primary α-substituent as methyl, conjugate addition of **1a** to the (*Z*)-geometric isomers **2c**–**2g** proceeded with comparably lower levels of reactivity (entries 8–12 versus entries 1–4 and Table 1, entry 6). As with the other 2-ethyl-3-nitropropionate substrates **3**, addition to (*Z*)-**2i** and (*Z*)-**2j** also proved challenging with diminished yields and selectivities being witnessed (entries 13 and 14). Notably, the major enantiomers obtained from conjugate additions to (*E*)-**2** or (*Z*)-**2** were determined to have *R*-configuration in all cases. The scalability of the method was demonstrated on a 1.0 g scale of (*E*)-**2c** using phenylboronic acid (**1a**). (*R*)-1,1-Methyl-1-phenyl-3-nitropropionate (**3ac**) was isolated in 55% yield with 99% ee (entry 15), consistent with the small scale result reported in Table 1, entry 6.

Table 4. Asymmetric addition of phenylboronic acid (**1a**) to β-nitroacrylates **2**[a]

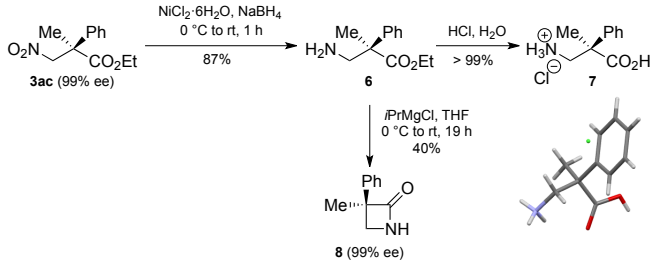


1a **2** **3**

Entry	**2**	Time (h)	**3** (%)[b]	ee (%)[c]
1	R^1 = Me, R^2 = Me [(*E*)-**2d**]	3	32 (**3ad**)	99
2	R^1 = Me, R^2 = *i*Pr [(*E*)-**2e**]	3	34 (**3ae**)	99
3	R^1 = Me, R^2 = *t*Bu [(*E*)-**2f**]	3	32 (**3af**)	99[d]
4	R^1 = Me, R^2 = Bn [(*E*)-**2g**]	3	20 (**3ag**)	99
5	R^1 = Me, R^2 = 2,6-DMP[e] [(*E*)-**2h**]	3	41 (**3ah**)	99
6	R^1 = Et, R^2 = Me [(*E*)-**2i**]	12	33 (**3ai**)	84
7	R^1 = Et, R^2 = Et [(*E*)-**2j**]	12	23 (**3aj**)	73
8	R^1 = Me, R^2 = Et [(*Z*)-**2c**]	12	36 (**3ac**)	86
9	R^1 = Me, R^2 = Me [(*Z*)-**2d**]	12	42 (**3ad**)	96
10	R^1 = Me, R^2 = *i*Pr [(*Z*)-**2e**]	12	38 (**3ae**)	86
11	R^1 = Me, R^2 = *t*Bu [(*Z*)-**2f**]	12	26 (**3af**)	91[d]
12[f]	R^1 = Me, R^2 = Bn [(*Z*)-**2g**]	12	19 (**3ag**)	73
13	R^1 = Et, R^2 = Me [(*Z*)-**2i**]	12	18 (**3ai**)	77
14[g]	R^1 = Et, R^2 = Et [(*Z*)-**2j**]	12	19 (**3aj**)	73
15[h]	R^1 = Me, R^2 = Et [(*E*)-**2c**]	7	55 (**3ac**)	99

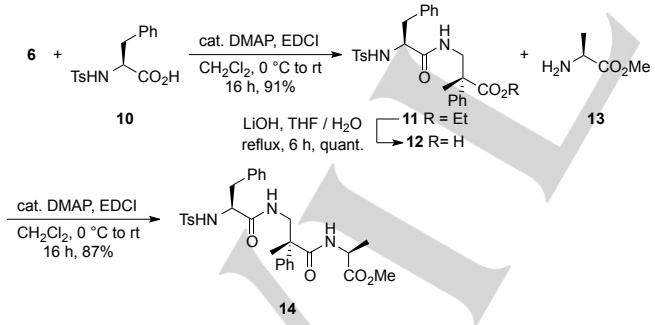
[a] Conducted in toluene (0.8 mL) using β-nitroacrylates **2** (0.2 mmol), phenylboronic acid (**1a**) (0.6 mmol, 3.0 equiv based on **2c**) and KHF_2 (3.0 M, 0.4 mL, 1.2 mmol) in the presence of rhodium catalyst prepared in situ from $[RhCl(C_2H_4)_2]_2$ (5.0 μmol, 5 mol% Rh) and chiral diene **L1** (12 μmol, 6.0

mol%); reactions were worked up when TLC indicated completion, or at 12 h, whichever came first; ratios of regioisomers **3**/**5** ranged 0.7–2.6, as determined by ^{1}H NMR spectroscopic analysis of crude mixture. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The ee was determined by converting **3af** into **3ad**. [e] 2,6-Dimethylphenyl. [f] 46% of (*E*)-**2g** and 24% of (*Z*)-**2g** were isolated, respectively. [g] 38% of (*E*)-**2j** and 16% of (*Z*)-**2j** were isolated, respectively. [h] Conducted on a 1.0 g (6.4 mmol) scale.



Scheme 2. Syntheses of β^{2,2}-amino acid **7** and β^{2,2}-lactam **8**

To demonstrate the utility of the method, the syntheses of a β^{2,2}-amino acid and a β^{2,2}-lactam were conducted. Treatment of 3-nitropropionate **3ac** with in situ-generated nickel boride afforded β-amino ester **6** in 87% yield, from which β^{2,2}-amino acid **7** was obtained in quantitative yield upon acid-catalyzed hydrolysis (Scheme 2). Single crystal X-ray analysis of **7** unambiguously confirmed that the absolute configuration was *R*. Base-promoted cyclization[13] of β-amino ester **6**, on the other hand, furnished chiral α,α-disubstituted β-lactam **8** in 40% yield, notably without the loss of the high ee of precursor **3ac**. Further demonstration of the utility of our method was obtained by the synthesis of a tripeptide consisting of a β^{2,2}-amino acid and α-amino acids (Scheme 3). Dipeptide **11** was obtained in 91% yield from amide bond formation between β-amino ester **6** and *N*-tosyl-protected L-phenylalanine **10** under standard reaction conditions.[14] Coupling of acid **12**, obtained following the base hydrolysis of **11**, with L-alanine methyl ester (**13**) furnished tripeptide **14** in 87% yield.



Scheme 3. Syntheses of tripeptide **14** comprising a β^{2,2}-amino acid

To understand the observed stereochemical outcome of the addition reaction, DFT calculations employing the restricted M06L method[15] with Ahlrichs' basis set[16] were performed using the Gaussian 09 program.[17] As depicted in Figure 1, these calculations indicated that coordination of the Rh(I) center to the *Re*-face of (*E*)-**2d** in complex **9a**, which would give rise to the observed product (*R*)-**3ad**, was preferred by 3.3 kcal/mol over the corresponding *Si*-face-coordinated complex **9b** due to repulsion between the nitro group and the 1-naphthyl group of the ligand backbone. Furthermore, complex **9a**, where the ester group directs away from the ligand substituent, explains the high stereoselectivity observed for the addition to (*E*)-substrates containing distinct ester groups (Table 3, entries 1–5).

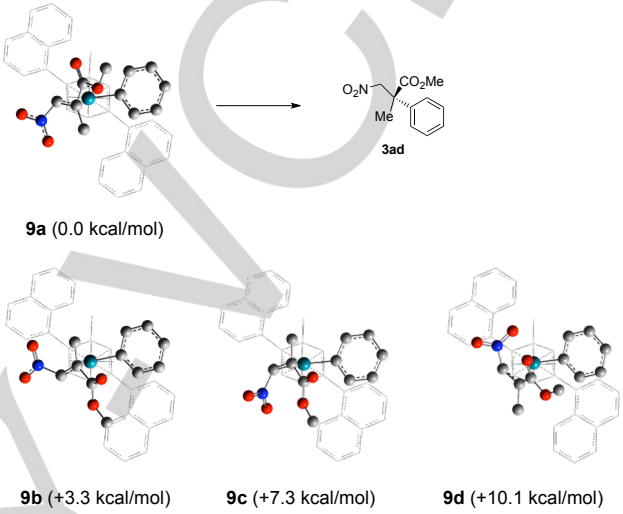


Figure 1. DFT optimized stereochemical structures and energy diagrams of the putative intermediates of (*E*)-**2d** and (*Z*)-**2d**, and Rh(I)/**L1**

In contrast to that observed empirically, however, according to the calculations coordination of the Rh(I) center to the *Re*-face of (*Z*)-**2d** (complex **9d**), that would lead to the (*R*)-product, is disfavored over the corresponding *Si*-face coordination complex **9c**, that would afford the (*S*)-product, by 2.8 kcal/mol. This discrepancy between the calculated and observed stereoselectivity can be explained by in situ isomerization of the (*Z*)-isomers to the (*E*)-isomers. Indeed, this was supported by the observation that the crude ^{1}H NMR spectra from the reactions of (*Z*)-substrates comprised mixtures of unreacted (*Z*)-nitroacrylates as well as their (*E*)-isomers. This phenomenon was particularly evident in the conjugate addition reaction of (*Z*)-**2g** (Table 3, entry 12) where purification of the crude product mixture yielded 24% of unreacted (*Z*)-**2g** and 46% of (*E*)-**2g**. Similarly, in the case of (*Z*)-**2j** (entry 14), 38% of (*E*)-**2j** and 16% of unreacted (*Z*)-**2j** were isolated following termination of the reaction. The driving force for the isomerization might be explained by the calculated energies of both **9c** and **9d** being greater than that of **9a** by 7.3 and 10.1 kcal/mol, respectively. Moreover, calculations show that the (*E*)-isomer, (*E*)-**2d**, is 2.3 kcal/mol lower in energy than its (*Z*)-isomer, (*Z*)-**2d**. The generally much lower ees observed in conjugate additions to the (*Z*)-nitroacrylates (Table 4, entries 8 and 10–14), as compared to addition to the corresponding (*E*)-nitroacrylates, is consistent with incomplete (*Z*)- to (*E*)-isomerization during the reaction.

Conclusions

In conclusion, the enantioselective 1,4-conjugate addition reaction of arylboronic acids to α-substituted β-nitroacrylates in the presence of Rh(I)-catalysts comprising chiral diene ligands has been reported for the first time. Chiral diene ligand **L1** was found to give the best results. While the corresponding 1,4-conjugate addition reaction to β-nitroolefins that we reported[7d] earlier displayed excellent results,[7d] the moderate regioselectivies and the relatively modest yields in the current study clearly show that α-substituted β-nitroacrylates are considerably more challenging substrates. In fact, this and the fact that related ligands **L9**–**L13** failed to provide any product in the presence of Rh(I) might explain the absence of prior publications for this conversion employing variants of the Hayashi−Miyaura reaction. Despite this, the stereoselectivities achieved in the study described herein were generally high to very high (up to 99% ee) and the method tolerated a host of arylboronic acids as nucleophile donors, providing (*R*)-configured α,α-disubstituted β-nitropropionates. Screening studies showed that a diverse range of bases and solvents could be used, and this might prove useful when optimizing the reaction conditions for a specific set of reactants and their target. The conjugate addition to (*E*)- and (*Z*)-α-substituted β-nitroacrylates both furnished (*R*)-configured products, contrary to that anticipated based on *in silico* analysis. This is explained by in situ geometric isomerization, driven by the higher thermodynamic stability of the (*E*)-isomer, before the Rh(I)-catalyzed asymmetric reaction takes place.

Finally, the utility of the reaction was demonstrated by the synthesis of non-proteinogenic $\beta^{2,2}$-amino acid **7** that contains a chiral, all-carbon quaternary center; obtained from α,α-disubstituted β-nitropropionate **3ac**. Additionally, conversion of **3ac** to $\beta^{2,2}$-lactam **8** and the conversation of β-amino ester **6** to tripeptide **14** were established. Studies towards the development of a catalytic system that can enhance the chemical yields of this transformation are currently under investigation in our laboratory.

Experimental Section

General

All commercial chemicals and solvents were reagent grade and were distilled before use. All reactions were carried out under an atmosphere of argon or nitrogen gas. Reactions were monitored by TLC using Merck 60 F 254 silica gel plates; zones were detected visually under ultraviolet irradiation (254 nm) or by spraying with $KMnO_4$ solution followed by heating with a heat gun or on a hot plate. Column chromatography was conducted over silica gel. NMR spectra were recorded at room temperature in deuterated solvents on Bruker spectrometers. Chemical shifts δ were recorded in parts per million (ppm) and were reported relative to the deuterated solvent signal for ^{13}C NMR spectroscopy or the residual ^{1}H-solvent signal for ^{1}H NMR spectroscopy. First order spin multiplicities are abbreviated as singlet (s), doublet (d), triplet (t), quadruplet (q), doublet of doublets (dd) and septet (sep); multiplets are abbreviated as (m). High-resolution mass spectra were obtained using EI and ESI ionization methods. Optical rotations were measured on a Jasco P-2000 polarimeter. Enantiomeric excessed were determined by HPLC analysis on Chiralpak AD-H, AS-H, or IA columns, or on a Chiralcel OJ-H column (Daicel Chemical Industries, Ltd). Boronic acids **1** that were commercially available were used as supplied and/or were prepared using methods reported in the literature.[18] Substrates **2** were prepared according to the literature.[4d,4g,19] Chiral diene ligands **L1-L8**[7a] and **L12**[12d] were prepared according to the reported procedure; ligands **L9**–**L13** are commercially available.

General procedures for rhodium-catalyzed 1,4-addition reactions: Under a N_2 atmosphere, to a mixture of $[RhCl(C_2H_4)_2]_2$ (1.93 mg, 5.0 *μ*mol, 5.0 mol% of Rh), chiral ligand **L1** (4.63 mg, 12.0 *μ*mol, 6.0 mol%), phenylboronic acid **1a** (0.6 mmol, 3.0 equiv) and (*E*)-nitroacrylate **2c** (0.2 mmol, 1.0 equiv) was added toluene (0.8 mL) and aqueous KHF_2 (3.0 M, 0.4 mL, 1.2 mmol, 6.0 equiv). The resulting mixture was heated to 40 °C. After TLC indicated completion, or at 24 h, whichever came first, the product mixture was concentrated in vacuo and the residue was purified by column chromatography over silica gel (hexanes / ethyl acetate, 50 / 1 to 3 / 1) to afford the desired product **3ac** (25.1 mg, 53% yield) as a colorless oil.

(*R*)-Ethyl 2-methyl-3-nitro-2-phenylpropanoate (3ac)
R_f 0.65 (hexanes / ethyl acetate, 3 / 1). On a 1.0 g reaction scale, 830 mg 55% yield, of **3ac** was isolated. Ee was determined on a Daicel Chiralpak AS-H column (250 mm) eluting with hexanes / 2-propanol, 95 / 5, flow = 1.0 mL/min; retention times: 11.36 min ((*S*)-enantiomer) and 13.09 min ((*R*)-enantiomer). 99% ee; $[\alpha]_D^{27}$ +29.7 (*c* 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.40–7.30 (m, 5H), 5.19 (d, *J* = 13.4 Hz, 1H), 4.69 (d, *J* = 13.4 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.79 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 172.5, 138.5, 129.0, 128.2, 125.8, 81.9, 62.0, 49.8, 20.9, 13.9; FT-IR (KBr, neat): $\tilde{\nu}$ 2980, 2930, 1734, 1557, 1456, 1378, 1227, 1128, 1022, 868, 770, 702, 661, 606, 536 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}NO_4$ [*M*] 237.1001, found 237.1000.

Reduction of 3ac: To a suspension of **3ac** (39.2 mg, 0.17 mmol) and $NiCl_2{\bullet}6H_2O$ (40.0 mg, 0.17 mmol) in MeOH (1.3 mL) was added $NaBH_4$ (32.3 mg, 0.85 mmol) at 0 °C and the mixture was stirred at rt for 1 h. The mixture was quenched with sat. $NH_4Cl_{(aq)}$ at 0 °C and extracted with CH_2Cl_2 (5 mL ×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with MeOH / CH_2Cl_2, 1 / 10) to afford product **6** (29.8 mg, 87%) as an orange liquid.

(*R*)-Ethyl 3-amino-2-methyl-2-phenylpropanoate (6)
R_f 0.10 (hexanes / ethyl acetate, 1 / 1); $[\alpha]_D^{17}$ +10.9 (*c* 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.37–7.31 (m, 3H), 7.29–7.23 (m, 2H), 4.23–4.12 (m, 2H), 3.17 (d, *J* = 13.4 Hz, 1H), 3.03 (d, *J* = 13.4 Hz, 1H), 1.65 (br, 2H), 1.60 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 175.6, 141.6, 128.6, 127.0, 126.2, 60.8, 52.7, 51.1, 21.0, 14.1; FT-IR (KBr, neat): $\tilde{\nu}$ 3378, 2971, 2930, 1724, 1456, 1379, 1249, 1147, 1024, 863, 762, 699 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{18}NO_2$ [$M + H^+$] 208.1338, found 208.1339.

Hydrolysis of 6: To **6** (30.0 mg, 0.15 mmol) was added 6 *N* HCl (1.0 mL) and the mixture was stirred at 80 °C overnight. Water was then removed under reduced pressure to give **7** (26.8 mg, quant.) as a white solid.

(*R*)-3-Amino-2-methyl-2-phenylpropanoic acid hydrochloride (7)
Mp 282–283 °C; $[\alpha]_D^{21}$ +29.5 (*c* 1.00 in H_2O); ^{1}H NMR (400 MHz, D_2O): *δ* 7.54–7.49 (m, 2H), 7.46–7.41 (m, 3H), 3.46 (s, 2H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, D_2O): *δ* 178.1, 138.3, 129.4, 128.6, 126.4, 49.0, 46.9, 20.4. HRMS (ESI) *m*/*z* calcd for $C_{10}H_{14}NO_2$ [$M + H^+$] 180.1025, found 180.1024.

Synthesis of 8: To a solution of **6** (56.0 mg, 0.27 mmol) in dry THF (1.0 mL) was added ^{i}PrMgCl (2.0 M in THF, 0.67 mL, 1.35 mmol) dropwise from a syringe at 0 °C. The resulting reaction mixture was stirred at rt for 19 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5.0 mL) and extracted with ethyl acetate (8 mL ×3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and the volatiles were removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with ethyl acetate / hexanes, 1.5 / 1) to give **8** (17.4 mg, 40%) as a yellow liquid.

(*R*)-3-Methyl-3-phenylazetidin-2-one (8)
R_f 0.25 (hexanes / ethyl acetate, 1 / 1). Ee was determined on a Daicel Chiralcel OJ-H column (250 mm) eluting with hexanes / 2-propanol, 60 / 40, flow = 1.0 mL/min; retention times: 5.97 min ((*S*)-enantiomer) and 6.77 min ((*R*)-enantiomer). > 99.5% ee; $[\alpha]_D^{27}$ −2.6 (*c* 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.45–7.40 (m, 2H), 7.38–7.32 (m, 2H), 7.30–7.23 (m, 1H), 3.60 (d, *J* = 5.2 Hz, 1H), 3.46 (d, *J* = 5.2 Hz, 1H), 1.71 (s, 3H), 1.59 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 172.6, 140.8, 128.7, 127.1, 125.9, 60.3, 51.1, 23.5; FT-IR (KBr, neat): $\tilde{\nu}$ 3938, 3855, 3446, 3336, 3024, 2925, 1739, 1647, 1024, 667, 509, 461 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{10}H_{12}NO$ [*M* + H$^+$] 162.0919, found 162.0919.

Synthesis of 11: To a solution of *N*-tosyl-protected L-phenylalanine **10** (31.9 mg, 0.10 mmol) and **6** (25.9 mg, 0.13 mmol) in dry CH_2Cl_2 (1.0 mL) were added DMAP (1.2 mg, 0.01 mmol) and EDCI•HCl (20.0 mg, 0.10 mmol) at 0 °C. After 1 h the reaction temperature was warmed to rt. After being stirred overnight, the reaction mixture was diluted with CH_2Cl_2, and the organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography over silica gel (eluting with hexanes / ethyl acetate, 3 / 1) to afford product **11** (46.3 mg, 91%) as a white solid.

(*R*)-Ethyl 2-methyl-3-((*S*)-2-(4-methylphenylsulfonamido)-3-phenylpropanamido)-2-phenylpropanoate (11)
R_f 0.80 (ethyl acetate); mp 123–124 °C; $[\alpha]_D^{30}$ −17.6 (*c* 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.46 (d, *J* = 8.2 Hz, 2H), 7.36–7.29 (m, 2H), 7.29–7.20 (m, 3H), 7.20–7.09 (m, 5H), 6.87 (d, *J* = 6.9 Hz, 3H), 4.77 (d, *J* = 6.0 Hz, 1H), 4.29–4.08 (m, 2H), 3.76 (dd, *J* = 6.0, 13.8 Hz, 1H), 3.60 (qd, *J* = 7.2, 13.8 Hz, 2H), 2.94 (dd, *J* = 6.0, 14.0 Hz, 1H), 2.75 (dd, *J* = 8.0, 14.0 Hz, 1H), 2.41 (s, 3H), 1.52 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 175.4, 170.1, 143.8, 140.9, 135.5, 135.2, 129.7, 129.0, 128.9, 128.6, 127.3, 127.19, 127.16, 125.9, 61.4, 58.0, 51.7, 47.3, 38.3, 21.5, 20.5, 14.0; FT-IR (KBr, neat): $\tilde{\nu}$ 3268, 2986, 2937, 1719, 1664, 1453, 1330, 1251, 1158, 1092, 1025, 947, 813, 753, 699, 669, 554 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{33}N_2O_5S$ [*M* + H$^+$] 509.2110, found 509.2111.

Hydrolysis of 11: To a solution of **11** (25.4 mg, 0.05 mmol) in THF / H_2O (4 / 1, *v* / *v*, 1.0 mL), LiOH (3.6 mg, 0.15 mmol) was added at rt. The reaction mixture was heated to reflux for 6 h, and then the volatiles were removed under reduced pressure. The residue was diluted with distilled H_2O and the aqueous layer was washed with diethyl ether. The aqueous phase was concentrated to give the amino acid **12** (25.0 mg, quant.) as a white solid.

(*R*)-2-Methyl-3-((*S*)-2-(4-methylphenylsulfonamido)-3-phenylpropanamido)-2-phenylpropanoic acid (12)
Mp 237–239 °C (decomposed); $[\alpha]_D^{30}$ +22.5 (*c* 1.00 in H_2O); ^{1}H NMR (400 MHz, D_2O): *δ* 7.41–7.33 (m, 2H), 7.30–7.22 (m, 3H), 7.21–7.10 (m, 5H), 7.06–7.02 (m, 2H), 7.01–6.93 (m, 2H), 3.54–3.47 (m, 2H), 3.44 (d, *J* = 13.3 Hz, 1H), 3.15 (d, *J* = 13.3 Hz, 1H), 2.75–2.65 (m, 1H), 2.57–2.43 (m, 1H), 2.27 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, D_2O): *δ* 183.3, 177.4, 143.1, 141.3, 140.4, 138.7, 129.4, 129.2, 128.5, 128.2, 126.8, 126.7, 126.2, 125.7, 61.4, 52.5, 47.5, 41.2, 21.2, 20.4. HRMS (ESI) *m*/*z* calcd for $C_{26}H_{29}N_2O_5S$ [*M* + H$^+$] 481.1797, found 481.1794.

Synthesis of 14: To a solution of carboxylic acid **12** (45.5 mg, 0.09 mmol) and L-alanine methyl ester hydrochloride **13** (12.2 mg, 0.12 mmol) in dry CH_2Cl_2 (1.0 mL) was added DMAP (1.1 mg, 0.01 mmol) and EDCI•HCl (18.1 mg, 0.09 mmol) at 0 °C. After 1 h the reaction temperature was warmed up to rt. After being stirred overnight, the reaction mixture was diluted with CH_2Cl_2 and the organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography over silica gel (eluting with hexanes / ethyl acetate, 3 / 1) to afford product **14** (46.6 mg, 87%) as a white solid.

(*S*)-Methyl 2-((*R*)-2-methyl-3-((*S*)-2-(4-methylphenylsulfonamido)-3-phenylpropanamido)-2-phenylpropanamido)propanoate (14)
R_f 0.70 (ethyl acetate); mp 49–50 °C; $[\alpha]_D^{30}$ −47.0 (*c* 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.47 (d, *J* = 8.2 Hz, 2H), 7.40–7.29 (m, 5H), 7.18–7.05 (m, 5H), 6.93 (d, *J* = 7.1 Hz, 2H), 5.77 (d, *J* = 7.2 Hz, 1H), 5.11 (d, *J* = 7.2 Hz, 1H), 4.54 (quintet, *J* = 7.3 Hz, 1H), 3.87 (dd, *J* = 7.3, 13.4 Hz, 1H), 3.72 (s, 3H), 3.65 (dd, *J* = 5.4, 13.6 Hz, 1H), 3.47 (dd, *J* = 7.4, 13.6 Hz, 1H), 2.97 (dd, *J* = 5.9, 14.0 Hz, 1H), 2.84 (dd, *J* = 7.7, 14.0 Hz, 1H), 2.39 (s, 3H), 1.47 (s, 3H), 1.33 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 175.7, 173.6, 170.3, 143.5, 141.1, 136.1, 135.4, 129.6, 129.2, 128.8, 128.7, 127.7, 127.1, 127.0, 126.8, 58.1, 52.5, 51.6, 48.3, 47.3, 38.7, 22.4, 21.5, 17.5; FT-IR (KBr, neat): $\tilde{\nu}$ 3337, 3022, 2993, 2943, 1739, 1661, 1521, 1449, 1331, 1221, 1162, 1091, 949, 813, 754, 700, 667, 554 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{36}N_3O_6S$ [*M* + H$^+$] 566.2325, found 566.2325.

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Keywords: conjugate addition • $\beta^{2,2}$-amino acid • rhodium • chiral diene • enantioselective synthesis

[1] F. Kudo, A. Miyanaga, T. Eguchi, *Nat. Prod. Rep.* **2014**, *31*, 1056–1073.

[2] a) R. B. Morin, M. Gorman, *Chemistry and Biology of β-Lactam Antibiotics*; Academic Press: New York, **1982**; Vols. 1–3; b) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437–4492; c) R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219–3232; d) D. Seebach, J. Gardiner, *Acc. Chem. Res.* **2008**, *41*, 1366–1375.

[3] a) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991−8035; b) J.-A. Ma, *Angew. Chem. Int. Ed.* **2003**, *42*, 4290−4299; *Angew. Chem.* **2003**, *115* 4426−4435; c) N. Sewald, *Angew. Chem. Int. Ed.* **2003**, *42*, 5794−5795; *Angew. Chem.* **2003**, *115*, 5972−5973; d) G. Lelais, D. Seebach, *Biopolymers* **2004**, *76*, 206−243; e) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; E. Juaristi, V. A. Soloshonok, Eds.; Wiley-VCH: New York, **2005**; f) D. Seebach, A. K. Beck, S. Capone, G. Deniau, U. Grošelj, E. Zass, *Synthesis* **2009**, 1−32; g) B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2010**, *39*, 1656−1691; h) K. Mikami, S. Fustero, M. Sánchez-Roselló, J. L. Aceña, V. Soloshonok, A. Sorochinsky, *Synthesis* **2011**, 3045−3079.

[4] a) A. Rimkus, N. Sewald, *Org. Lett.* **2003**, *5*, 79−80; b) U. Eilitz, F. Leßmann, O. Seidelmann, V. Wendisch, *Tetrahedron: Asymmetry* **2003**,

14, 189−191; c) U. Eilitz, F. Leßmann, O. Seidelmann, V. Wendisch, *Tetrahedron: Asymmetry* **2003**, *14*, 3095−3097; d) M. A. Swiderska, J. D. Stewart, *Org. Lett.* **2006**, *8*, 6131−6133; e) K. Wakabayashi, K. Aikawa, S. Kawauchi, K. Mikami, *J. Am. Chem. Soc.* **2008**, *130*, 5012−5013; f) S.-L. Zhu, S.-Y. Yu, D.-W. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 545−548; *Angew. Chem.* **2008**, *120*, 555−558; g) N. J. A. Martin, X. Cheng, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 13862−13863; h) A. Petri, O. Seidelmann, U. Eilitz, F. Leßmann, S. Reißmann, V. Wendisch, A. Gutnov, *Tetrahedron Lett.* **2014**, *55*, 267–270.

[5] a) H.-H. Lu, F.-G. Zhang, X.-G. Meng, S.-W. Duan, W.-J. Xiao, *Org. Lett.* **2009**, *11*, 3946–3949; b) F.-G. Zhang, Q.-Q. Yang, J. Xuan, H.-H. Lu, S.-W. Duan, J.-R. Chen, W.-J. Xiao, *Org. Lett.* **2010**, *12*, 5636–5639; c) R. Kastl, H. Wennemers, *Angew. Chem. Int. Ed.* **2013**, *52*, 7228–7232; *Angew. Chem.* **2013**, *125*, 7369–7373; d) J.-Q. Weng, Q.-M. Deng, L. Wu, K. Xu, H. Wu, R.-R. Liu, J.-R. Gao, Y.-X. Jia, *Org. Lett.* **2014**, *16*, 776−779; e) K. Mori, M. Wakazawa, T. Akiyama, *Chem. Sci.* **2014**, *5*, 1799–1803; f) Y. Zhong, S. Ma, Z. Xu, M. Chang, R. Wang, *RSC Adv.* **2014**, *4*, 49930–49933; g) H. Wu, R.-R. Liu, C. Shen, M.-D. Zhang, J.-R. Gao, Y.-X. Jia, *Org. Chem. Front.* **2015**, *2*, 124–126; h) S.-W. Chen, Q.-X. Lou, Y.-Y. Ding, S.-S. Zhang, W.-H. Hu, J.-L. Zhao, *Adv. Synth. Catal.* **2015**, *357*, 2437–2441.

[6] a) M. Sakai, H. Hayashi, N. Miyaura, *Organometallics* **1997**, *16*, 4229–4231; b) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169–196; c) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829–2844; d) T. Hayashi, *Pure Appl. Chem.* **2004**, *76*, 465–475; e) H. J. Edwards, J. D. Hargrave, S. D. Penrose, C. G. Frost, *Chem. Soc. Rev.* **2010**, *39*, 2093–2105.

[7] a) W.-T. Wei, J.-Y. Yeh, T.-S. Kuo, H.-L. Wu, *Chem. Eur. J.* **2011**, *17*, 11405–11409; b) C.-C. Liu, D. Janmanchi, C.-C. Chen, H.-L. Wu, *Eur. J. Org. Chem.* **2012**, 2503–2507; c) Y.-C. Chung, D. Janmanchi, H.-L. Wu, *Org. Lett.* **2012**, *14*, 2766–2769; d) K.-C. Huang, B. Gopula, T.-S. Kuo, C.-W. Chiang, P.-Y. Wu, J. P. Henschke, H.-L. Wu, *Org. Lett.* **2013**, *15*, 5730–5733; e) B. Gopula, Y.-F. Tsai, T.-S. Kuo, P.-Y. Wu, J. P. Henschke, H.-L. Wu, *Org. Lett.* **2015**, *17*, 1142–1145; f) B. Gopula, S.-H. Yang, T.-S. Kuo, J.-C. Hsieh, P.-Y. Wu, J. P. Henschke, H.-L. Wu, *Chem. Eur. J.* **2015**, *21*, 11050–11055; g) J.-H. Fang, C.-A. Chang, B. Gopula, T.-S. Kuo, P.-Y. Wu, J. P. Henschke, H.-L. Wu, *Asian J. Org. Chem.* **2016**, *5*, 481–485.

[8] a) T. Hayashi, T. Senda, M. Ogasawara, *J. Am. Chem. Soc.* **2000**, *122*, 10716–10717; b) J. G. Boiteau, R. Imbos, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 681–684; c) A. Duursma, R. Hoen, J. Schuppan, R. Hulst, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 3111–3113; d) A. Duursma, D. Peña, A. J. Minnaard, B. L. Feringa, *Tetrahedron: Asymmetry* **2005**, *16*, 1901–1904; e) L. Dong, Y.-J. Xu, L.-F. Cun, X. Cui, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Org. Lett.* **2005**, *7*, 4285–4288; f) L. Dong, Y.-J. Xu, W.-C. Yuan, X. Cui, L.-F. Cun, L.-Z. Gong, *Eur. J. Org. Chem.* **2006**, 4093–4105; g) Z.-Q. Wang, C.-G. Feng, S.-S. Zhang, M.-H. Xu, G.-Q. Lin, *Angew. Chem. Int. Ed.* **2010**, *49*, 5780–5783; *Angew. Chem.* **2010**, *122*, 5916–5919; h) F. Lang, G.-H. Chen, L.-C. Li, J.-W. Xing, F.-Z. Han, L.-F. Cun, J. Liao, *Chem. Eur. J.* **2011**, *17*, 5242–5245; i) J.-W. Xing, G.-H. Chen, P. Cao, J. Liao, *Eur. J. Org. Chem.* **2012**, 1230–1236; j) F. Xue, D.-P. Wang, X.-C. Li, B.-S. Wan, *J. Org. Chem.* **2012**, *77*, 3071–3081; k) X. Bao, Y.-X. Cao, W.-D. Chu, H. Qu, J.-Y. Du, X.-H. Zhao, X.-Y. Ma, C.-T. Wang, C.-A. Fan, *Angew. Chem. Int. Ed.* **2013**, *52*, 14167–14172; *Angew. Chem.* **2013**, *125*, 14417–14422.

[9] For seminal reviews on chiral diene ligands, see: a) F. Glorius, *Angew. Chem. Int. Ed.* **2004**, *43*, 3364–3366; *Angew. Chem.* **2004**, *116*, 3444–3446; b) J. B. Johnson, T. Rovis, *Angew. Chem. Int. Ed.* **2008**, *47*, 840–871; *Angew. Chem.* **2008**, *120*, 852–884; c) C. Defieber, H. Grützmacher, E. M. Carreira, *Angew. Chem. Int. Ed.* **2008**, *47*, 4482–4502; *Angew. Chem.* **2008**, *120*, 4558–4579; d) R. Shintani, T. Hayashi, *Aldrichimica Acta* **2009**, *42*, 31–38; e) C.-G. Feng, M.-H. Xu, G.-Q. Lin, *Synlett* **2011**, 1345–1356; f) P. Tian, H.-Q. Dong, G.-Q. Lin, *ACS Catal.* **2012**, *2*, 95–119; g) X.-Q. Feng, H.-F. Du, *Asian J. Org. Chem.* **2012**, *1*, 204–213.

[10] See the supporting information.

[11] a) R. Ballini, D. Fiorini, A. Palmieri, *Tetrahedron Lett.* **2004**, *45*, 7027–7029; b) R. Ballini, S. Gabrielli, A. Palmieri, M. Petrini, *Tetrahedron* **2008**, *64*, 5435–5441.

[12] a) Y. Otomaru, K. Okamoto, R. Shintani, T. Hayashi, *J. Org. Chem.* **2005**, *70*, 2503–2508; b) J.-F. Paquin, C. Defieber, C. R. J. Stephenson E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 10850–10851; c) S. Helbig, S. Sauer, N. Cramer, S. Laschat, A. Baro, W. Frey, *Adv. Synth. Catal.* **2007**, *349*, 2331–2337; d) S.-S. Jin, H. Wang, T.-S. Zhu, M.-H. Xu, *Org. Biomol. Chem.* **2012**, *10*, 1764–1768; e) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998** *120*, 5579–5580.

[13] H.-M. Li, B.-M. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732−733.

[14] a) S. Hanessian, H. Sailes, A. Munro, E. Therrien, *J. Org. Chem.* **2003**, *68*, 7219−7233; b) S. H. Kim, S. W. Kwon, S. Y. Chu, J. H. Lee, B. Narsaiah, C. H. Kim, S. K. Kang, N. S. Kang, S. D. Rhee, M. A. Bae, S. H. Ahn, D. C. Ha, K. Y. Kim, J. H. Ahn, *Chem. Pharm. Bull.* **2011**, *59*, 46−52; c) J. Kim, W. S. Lee, J. Koo, J. Lee, S. B. Park, *ACS Comb. Sci.* **2014**, *16*, 24−32.

[15] Y. Zhao, D. G. Truhlar, *J. Chem. Phys.* **2006**, *125*, 194101.

[16] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.

[17] Gaussian 09, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.

[18] A. S. Paraskar, A. Sudalai, *Tetrahedron* **2006**, *62*, 4907–4916.

[19] a) K. Jayakanthan, K. P. Madhusudanan, Y. D. Vankar, *Tetrahedron* **2004**, *60*, 397–403; b) Y. A. Volkova, E. B. Averina, Y. K. Grishin, V. B. Rybakov, T. S. Kuznetsova, N. S. Zefirov, *Tetrahedron Lett.* **2011**, *52*, 2910–2913; c) L.-A. Chen, X.-J. Tang, J.-W. Xi, W.-C. Xu, L. Gong, E. Meggers, *Angew. Chem. Int. Ed.* **2013**, *52*, 14021–14025; *Angew. Chem.* **2013**, *125*, 14271–14275.

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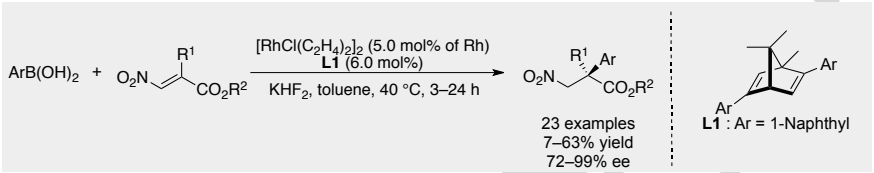

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The asymmetric conjugate addition of arylboronic acids to α-substituted β-nitroacrylates in the presence of 5 mol% of chiral Rh(I) catalysts afforded the corresponding α,α-disubstituted β-nitropropionates in up to 63% yield and 99% ee at 40 °C.