ChemPubSoc Europe

DOI: 10.1002/chem.201501059

CHEMISTRY A European Journal Full Paper

Organic Chemistry |Hot Paper|

Direct Synthesis of Chiral 3-Arylsuccinimides by Rhodium-Catalyzed Enantioselective Conjugate Addition of Arylboronic Acids to Maleimides

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Abstract: Chiral rhodium catalysts comprising 2,5-diaryl-substituted bicyclo[2.2.1]diene ligands **L1**–**L10** were utilized in the enantioselective 1,4-addition reaction of arylboronic acids to *N*-substituted maleimides. In the presence of 2.5 mol% of Rh^{I}/**L2**, enantioenriched conjugate addition adducts were isolated in 72–99% yields with 86–98% *ee*. This protocol offers a convenient method to access a variety of 3-arylsuccinimides in a highly enantioselective manner. Maleimides with readily cleavable *N*-protecting groups were tolerated enabling the synthesis of useful synthetic intermediates. Pyrrolidine **4**, a biologically active compound, and pyrrolidine **5**, an *ent*-precursor to an HSD-1 inhibitor, were synthesized to demonstrate the utility of this method.

Introduction

Optically active 3-substituted succinimide[1] and pyrrolidine[2] moieties can be found in biologically active molecules making their synthetic accessibility of relevance to both discovery and development chemists in the pharmaceutical industry. These compounds are commonly prepared from 2-substituted succinic acid derivatives which are themselves accessible from the diastereoselective alkylation of enolates, generated from chiral *N*-acyloxazolidinone imides, with *tert*-butyl bromoacetate,[3] and from the diastereoselective conjugate addition of alkyl radicals to fumarates controlled by a chiral 4-diphenylmethyl-2-oxazolidinone.[4] Additionally, chiral 2-substituted succinic acids can be obtained from a Rh-catalyzed enantioselective hydrogenation of 3-substituted itaconic acid derivatives[5] whilst 2-substituted succinic esters can similarly be obtained from maleate or fumarate esters.[6] More conveniently, however, the transition-metal-catalyzed conjugate addition of nucleophiles to *N*-substituted maleimides **1** offers a more direct and practical approach to chiral 3-substituted succinimides, which can then be converted into the corresponding 3-substituted pyrrolidine derivatives where required. In fact, asymmetric Rh-catalyzed conjugate addition reactions, that typically utilize organoboron reagents, have already been reported.[6a,7] Although axial chiral phosphorus-based ligands, such as BINAP,[8] P-PHOS,[9] and phosphoramidites[10] have been shown to promote high catalytic activity and enantioselectivity in the rhodium-catalyzed 1,4-addition of organoboronic acids to α,β-unsaturated carbonyl compounds, they performed relatively unselectively in the 1,4-addition of phenylboronic acid (**2a**) to *N*-methylmaleimide (28–51% *ee*).[6a] Similarly, only moderate to good *ee* values were witnessed when using rhodium catalysts comprising BINAP or phosphoramidite ligands in the 1,4-addition of boronic acid **2a** to 1-(2-*tert*-butylphenyl)maleimide.[7e] While the use of electron-deficient phosphorous-containing ligands provided improvements,[7h–i,k,11] giving optically active 3-substituted succinimides in 37–99% *ee*, the degree of selectivity was dependent on the *N*-substituent of the maleimide substrate.[7h]

The past decade has seen a significant increase in the number of chiral diene ligands as viable alternatives to traditional phosphine ligands due to their high activity and enantioinducing character in Rh-catalyzed C–C bond-forming processes. These ligands are often based on rigid, carbon-based bicyclic backbones.[12] While the asymmetric addition of a number of arylboronic acids to *N*-methyl, *N*-benzyl, and *N*-cyclohexylmaleimides in the presence of rhodium catalysts comprising chiral bicyclo[2.2.1]diene ligands gave the corresponding *N*-substituted 3-arylsuccinimides in up to 92% *ee*,[6a] excellent selectivity was observed when employing chiral

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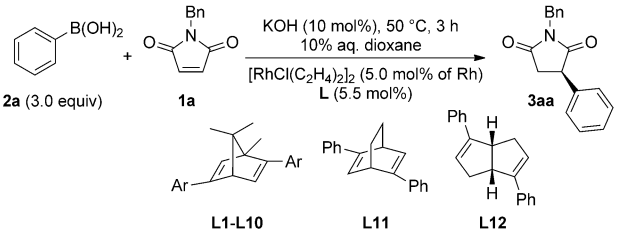
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201501059.

bicyclo[2.2.2]dienes instead.[7f] Despite these two reports, only a somewhat limited maleimide and boronic acid substrate scope has been reported to date using diene ligands, although chiral phosphine–olefin[7a–b] and sulfoxide–olefin[7g] hybrid ligands have also been reported as effective ligands in the preparation of optically active 3-substituted succinimides.

Previously we reported the design and synthesis of a novel family of chiral 2,5-diarylbicyclo[2.2.1]diene ligands, prepared from inexpensive (−)-bornyl acetate,[13a,b] that proved effective in a range of rhodium-catalyzed enantioselective addition reactions useful for the preparation of the synthetic intermediates of biologically active compounds.[13] These dienes exhibited not only a greater stability than their analogues derived from norbornadiene,[14] but also induced high enantioselectivity and catalytic activity in the presence of low loadings of Rh^{I} (TON up to 2000)[13b] in the 1,4-addition of organoboronic acids to linear[6b,13b,g] and cyclic[13c] α,β-unsaturated carbonyl compounds, and nitroolefins.[13d] We have also shown these ligands to be effective in Rh^{I}-catalyzed 1,2-addition reactions.[13e,f] In view of the utility of 3-substituted succinimides as synthetic building blocks, and given that examples of the use of chiral diene ligands in asymmetric 1,4-addition reactions of *N*-substituted maleimides are limited, we herein report the results of a thorough investigation of the use of Rh^{I}/2,5-diaryl bicyclo[2.2.1]diene catalysts in the enantioselective 1,4-addition of a variety of arylboronic acids to variously *N*-substituted maleimides.

Table 1. Substituent effect of chiral diene ligands.[a]



Entry	Ligand (Ar)	Yield [%][b]	*ee* [%][c]
1	**L1** (Ph)	86	93
2	**L2** (4-Me-C_6H_4)	94	96
3	**L3** (4-Ph-C_6H_4)	87	95
4	**L4** (4-*t*Bu-C_6H_4)	88	84
5	**L5** (1-naphthyl)	75	86
6	**L6** (2-naphthyl)	75	92
7	**L7** (4-NO_2-C_6H_4)	86	94
8	**L8** (4-F-C_6H_4)	75	95
9	**L9** (4-Cl-C_6H_4)	75	94
10	**L10** (4-CF_3-C_6H_4)	87	94
11	**L11**	trace	N.D.[d]
12	**L12**	N.R.[e]	N.D.[d]

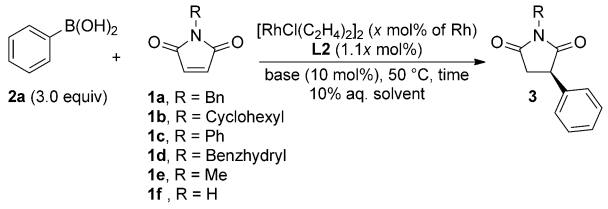
[a] The reaction was carried out in dioxane (2.0 mL) at 50 °C for 3 h by using **1a** (0.2 mmol) and **2a** (0.6 mmol, 3.0 equiv based on maleimide **1a** in the presence of rhodium catalysts generated in situ from $[RhCl(C_2H_4)_2]_2$ (5 μmol, 5 mol% of Rh) and chiral dienes (11 μmol, 5.5 mol%). [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral OD-H column. [d] Not determined. [e] No reaction.

Results and Discussion

The 2,5-substituent effect of the chiral bicyclo[2.2.1]dienes **L1**–**L10** in the Rh^{I}-catalyzed enantioselective addition of phenylboronic acid (**2a**) to *N*-benzylmaleimide (**1a**) was investigated first (Table 1). Reactions were conducted for 3 h at 50 °C, the product mixtures were chromatographically purified and the yields of the isolated 1,4-addition product **3aa** were used as a comparative measure of the activity between the catalysts. The desired succinimide product **3aa** was isolated in 86% yield and with 93% *ee* when the addition reaction was carried out using KOH (10 mol%) as the base in the presence of 5 mol% of the catalyst generated in situ from $[RhCl(C_2H_4)_2]_2$ and the phenyl-substituted ligand **L1** (Table 1, entry 1). Employment of the *para*-methylphenyl-substituted (tolyl) ligand **L2** or the *para*-biphenyl substituted ligand **L3** offered **3aa** in 94 and 87% yields and 96 and 95% *ee*, respectively (entries 2 and 3). However, carrying out the asymmetric reaction using the bulky *para*-(*tert*-butyl) substituted ligand **L4** (entry 4) or the 1-naphthyl substituted ligand **L5** (entry 5) resulted in diminished selectivity. By contrast, the 2-naphthyl-substituted chiral diene ligand **L6** provided a comparatively similar level of selectivity to the parent ligand **L1** (entry 6 vs. entry 1) although the yield was lower. Enantioinduction was slightly increased (94–95% *ee*) as compared to **L1** when the addition reaction was performed in the presence of ligands (**L7**–**L10**) containing electron-withdrawing substituents (entries 7–10), but yields were equal or reduced. When the asymmetric reaction was tested with commercially available chiral dienes with bicyclo[2.2.2] (**L11**) or bicyclo[3.3.0] (**L12**) frameworks, **3aa** was obtained in a trace amount or no product was detected at all, respectively (entries 11–12). From these investigations, the best catalytic activity and enantioselectivity was observed when employing 2,5-ditolyl-substituted ligand **L2**, and therefore subsequent reaction optimization was conducted using this ligand.

While comparable results were observed when carrying out the reaction at 50 °C for 3 h in THF, toluene (PhMe), or isopropanol (IPA) (Table 2, entries 1–3), giving rise to adduct **3aa** in 90–94% *ee*, and good yields (61–70%), and less pleasing results in EtOH, MeOH, or CH_2Cl_2 (entries 4–6), the reaction gave a significantly increased yield and *ee* when performed in dioxane (entry 7). For *N*-cyclohexylmaleimide (**1b**), the corresponding 3-phenylsuccinimide (**3ba**) was isolated in 99% yield and in 98% *ee* (entry 8), whereas the reactions of *N*-phenyl and *N*-benzhydrylmaleimides (**1c** and **1d**) proceeded less stereoselectively and less efficiently (entries 9 and 10). The asymmetric reaction of *N*-methylmaleimides (**1e**) provided addition product **3ea** in 74% yield and in 95% *ee* after 8 h (entry 11). Poignantly, but consistent with that witnessed previously,[7h] the conjugate addition of boronic acid **2a** to the unsubstituted substrate, maleimide **1f**, produced **3fa** in only 43% with 6% *ee* (entry 12) showing that the *N*-substituent plays a critical role in this reaction. This phenomenon may be due to *N*-deprotonation of maleimide resulting in its diminished electrophilicity, and perhaps coordination of the resultant anion to Rh^{I} leading to poisoning of the chiral catalyst. Inspection of entries 7–12 indicated that the *N*-substituent influenced stereoselectivity

Table 2. Optimization of reaction conditions.[a]



Entry	1	x [mol%]	Solvent	Base	t [h]	Yield [%][b]	ee [%][c]
1	**1a**	5.0	THF	KOH	3	63 (**3aa**)	90
2	**1a**	5.0	PhMe	KOH	3	61 (**3aa**)	94
3	**1a**	5.0	IPA	KOH	3	70 (**3aa**)	92
4	**1a**	5.0	EtOH	KOH	3	83 (**3aa**)	75
5	**1a**	5.0	MeOH	KOH	3	52 (**3aa**)	74
6	**1a**	5.0	CH_2Cl_2	KOH	3	30 (**3aa**)	97
7	**1a**	5.0	dioxane	KOH	3	94 (**3aa**)	96
8	**1b**	5.0	dioxane	KOH	3	99 (**3ba**)	98
9	**1c**	5.0	dioxane	KOH	2	91 (**3ca**)	86
10	**1d**	5.0	dioxane	KOH	6	84 (**3da**)	85
11	**1e**	5.0	dioxane	KOH	8	74 (**3ea**)	95
12	**1f**	5.0	dioxane	KOH	6	43 (**3fa**)	6
13	**1b**	5.0	dioxane	NaOH	3	98 (**3ba**)	97
14	**1b**	5.0	dioxane	K_2CO_3	3	98 (**3ba**)	96
15	**1b**	5.0	dioxane	Et_3N	24	N.R.[d]	N.D.[e]
16[f]	**1b**	5.0	dioxane	KOH	3	55 (**3ba**)	80
17[g]	**1b**	5.0	dioxane	KOH	3	$<$20 (**3ba**)	N.D.[e]
18	**1b**	2.5	dioxane	KOH	6	97 (**3ba**)	98
19	**1b**	2.0	dioxane	KOH	15	85 (**3ba**)	96
20	**1b**	1.0	dioxane	KOH	99	23 (**3ba**)	95

[a] The reaction was carried out in dioxane (2.0 mL) at 50 °C by using maleimides **1** (0.2 mmol) and boronic acid **2a** (0.6 mmol, 3.0 equiv based on **1**) in the presence of the rhodium catalyst generated in situ from $[RhCl(C_2H_4)_2]_2$ (5.0 μmol, 5 mol% of Rh) and chiral diene **L2** (11 μmol, 5.5 mol%). [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral OD-H column. [d] No reaction. [e] Not determined. [f] 2.0 equiv of **2a** was used. [g] 1.5 equiv of **2a** was used.

and reactivity, and that the best results were obtained for the *N*-benzyl, *N*-cyclohexyl, and *N*-methyl substituted maleimides **1a**, **1b**, and **1e**. Whilst the use of NaOH or K_2CO_3 as a base (entries 13 and 14) in place of KOH resulted in negligible impact on the yield and stereoselectivity, the use of Et_3N resulted in no **3ba** being formed within 24 h (entry 15). Although succinimide **3ba** was obtained in excellent yield and *ee* employing 3.0 equivalents of phenylboronic acid (**2a**) (entry 8), reducing this to 2.0 and 1.5 equivalents led to diminished chemical yields and *ee* values of **3ba** (entries 16 and 17). Reducing the amount of catalyst from 5 (entry 8) down to 2.5 mol% (entry 18) and 2.0 mol% (entry 19), on the other hand, provided a much smaller impact on catalytic activity and asymmetric induction. The impact on rate and *ee* was acceptable at 2.0 mol% (entry 19) but was exacerbated at 1.0 mol% of catalyst resulting in a disappointing 23% yield of addition adduct **3ba** being achieved in 99 h (entry 20), albeit with only a small reduction in enantioinduction (95% *ee*).

The asymmetric 1,4-addition of various arylboronic acids to *N*-cyclohexylmaleimide (**1b**) was explored using 2.5 mol% of catalyst under the optimum reaction conditions identified in Table 2, entry 18, to demonstrate the scope of the reaction (Table 3). High chemical yields (90–98%) and enantioselectivities (92–98% *ee*) were observed for all alkyl and electron-donating substituted arylboronic acids regardless of their substitution patterns (entries 1–9). While the asymmetric addition of 1-naphthylboronic acid (**2j**) gave the corresponding product **3bj** in 98% yield and in 90% *ee* after 19 h (entry 10), addition product **3bk** was isolated in 98% yield with 97% *ee* after 4 h of reaction of **1b** with 2-naphthylboronic acid (**2k**) (entry 11). Arylboronic acids bearing electron-withdrawing groups underwent addition in a high to highly enantioselective manner to give products **3bl**–**3bq** in 88–98% *ee* with good to excellent yields (72–96%, entries 8, 12–17). The absolute configuration of the newly formed stereogenic center was unambiguously determined to be *R* by single-crystal X-ray crystallography of succinimide **3bq** (Figure 1).

After having shown that electron-rich and -deficient arylboronic acids were tolerated in the 1,4-addition to *N*-cyclohexylmaleimide **1b**, attention was turned to maleimides bearing *N*-substituted protecting groups (Table 4). The conjugate addition of a diverse range of arylboronic acids to *N*-benzyl-protected maleimide **1a**, already proven to be a good electrophile in Table 2, and the addition product of which can be deprotected by hydrogenolysis,[6b] furnished the corresponding 1,4-addition adducts in good yields with good to high asymmetric induction (86–96% *ee*) (Table 4, entries 1–7). While a slightly lower selectivity was observed for 2-methyl-, 4-methyl-, and 4-fluorophenylboronic acids, the enantioselectivity was improved when conducting the reactions in the presence of 5 mol% of the Rh^I/**L2** catalyst (entries 2, 3, and 6). Variously substituted arylboronic acids underwent the addition reaction to *N*-(4-*me*-

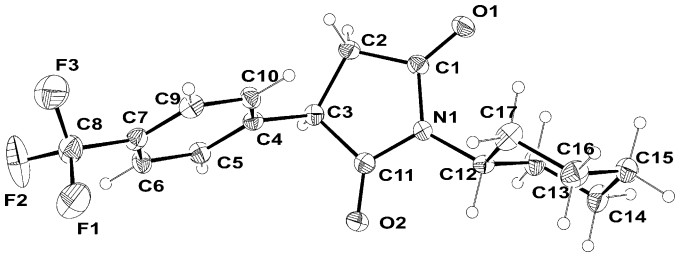
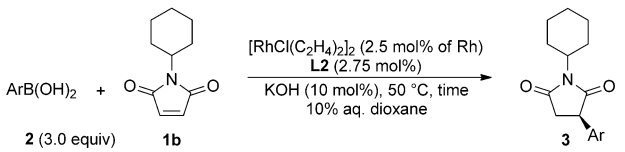


Figure 1. ORTEP plot of maleimide **3bq** with thermal ellipsoids drawn at the 30% level.

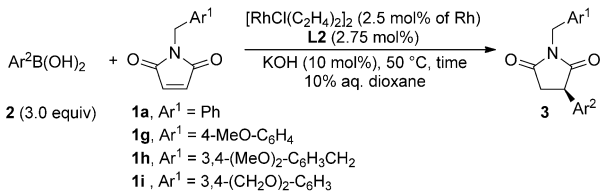
Table 3. Asymmetric conjugate addition of various arylboronic acids to *N*-cyclohexylmaleimide (**1b**).[a]



Entry	Ar	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph (**2a**)	6	97 (**3ba**)	98
2	2-Me-C_6H_4 (**2b**)	3	95 (**3bb**)	93
3	3-Me-C_6H_4 (**2c**)	3	98 (**3bc**)	92
4	4-Me-C_6H_4 (**2d**)	3	96 (**3bd**)	95
5	4-*t*Bu-C_6H_4 (**2e**)	3	93 (**3be**)	94
6	4-Ph-C_6H_4 (**2f**)	3	90 (**3bf**)	92
7	2,4-$(MeO)_2$-C_6H_3 (**2g**)	3	92 (**3bg**)	94
8	3-MeO-C_6H_4 (**2h**)	4	93 (**3bh**)	93
9	4-MeO-C_6H_4 (**2i**)	6	96 (**3bi**)	95
10	1-Naphthyl (**2j**)	19	98 (**3bj**)	90
11	2-Naphthyl (**2k**)	4	98 (**3bk**)	97
12	4-F-C_6H_4 (**2l**)	3	96 (**3bl**)	98
13	3-Cl-C_6H_4 (**2m**)	3	95 (**3bm**)	95
14	4-Cl-C_6H_4 (**2n**)	3	93 (**3bn**)	96
15	2-CF_3-C_6H_4 (**2o**)	3	72 (**3bo**)	90
16	3-CF_3-C_6H_4 (**2p**)	30	95 (**3bp**)	90
17	4-CF_3-C_6H_4 (**2q**)	3	89 (**3bq**)	88

[a] The reaction was carried out in dioxane (2.0 mL) at 50 °C using **1b** (0.2 mmol) and arylboronic acid **2** (0.6 mmol, 3.0 equiv based on **1b**) in the presence of the rhodium catalyst generated in situ from $[RhCl(C_2H_4)_2]_2$ (2.5 μmol, 2.5 mol% of Rh) and chiral diene **L2** (5.5 μmol, 2.75 mol%). [b] Yield of isolated product. [c] Determined by HPLC analysis using chiral columns.

Table 4. Asymmetric conjugate addition of various arylboronic acids to maleimides **1**.[a]



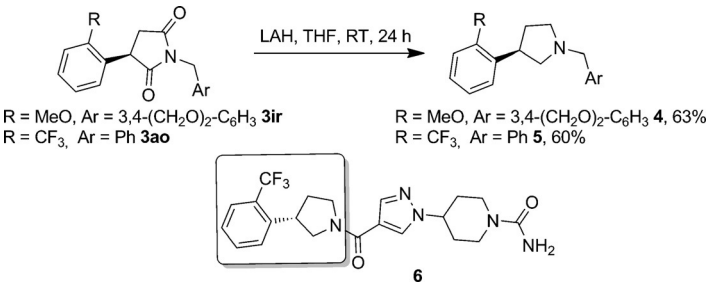
Entry	**1**	Ar^2	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	Ph (**2a**)	3	94 (**3aa**)	96
2[d]	**1a**	2-Me-C_6H_4 (**2b**)	4 (3)	91 (99) (**3ab**)	89 (97)
3[d]	**1a**	4-Me-C_6H_4 (**2d**)	5 (3)	91 (92) (**3ad**)	88 (95)
4	**1a**	3-MeO-C_6H_4 (**2h**)	5	90 (**3ah**)	91
5	**1a**	4-MeO-C_6H_4 (**2i**)	5	90 (**3ai**)	96
6[d]	**1a**	4-F-C_6H_4 (**2l**)	5 (2)	91 (98) (**3al**)	86 (95)
7	**1a**	2-CF_3-C_6H_4 (**2o**)	4	97 (**3ao**)	96
8	**1g**	Ph (**2a**)	6	98 (**3ga**)	93
9	**1g**	2-Me-C_6H_4 (**2b**)	4	93 (**3gb**)	97
10	**1g**	4-Me-C_6H_4 (**2d**)	4	98 (**3gd**)	89
11	**1g**	2,4-$(MeO)_2$-C_6H_3 (**2g**)	4	96 (**3gg**)	92
12	**1g**	3-MeO-C_6H_4 (**2h**)	4	90 (**3gh**)	96
13	**1g**	4-MeO-C_6H_4 (**2i**)	4	99 (**3gi**)	89
14	**1g**	4-F-C_6H_4 (**2l**)	4	97 (**3gl**)	91
15	**1h**	Ph (**2a**)	6	96 (**3ha**)	94
16	**1h**	2-Me-C_6H_4 (**2b**)	4	90 (**3hb**)	98
17	**1h**	4-Me-C_6H_4 (**2d**)	4	92 (**3hd**)	96
18	**1h**	2,4-$(MeO)_2$-C_6H_3 (**2g**)	4	90 (**3hg**)	91
19	**1h**	3-MeO-C_6H_4 (**2h**)	4	94 (**3hh**)	92
20	**1h**	4-MeO-C_6H_4 (**2i**)	4	99 (**3hi**)	94
21	**1h**	4-F-C_6H_4 (**2l**)	4	99 (**3hl**)	90
22	**1i**	2-MeO-C_6H_4 (**2r**)	4	99 (**3ir**)	92

[a] The reaction was carried out in dioxane (2.0 mL) at 50 °C for 3 h using maleimides **1** (0.2 mmol) and arylboronic acids **2** (0.6 mmol, 3.0 equiv based on **1**) in the presence of rhodium catalyst generated in situ from $[RhCl(C_2H_4)_2]_2$ (2.5 μmol, 2.5 mol% of Rh) and chiral diene **L2** (5.5 μmol, 2.75 mol%). [b] Yield of isolated product. [c] Determined by HPLC analysis using chiral columns. [d] The results shown in the parentheses were obtained by carrying out the reaction in the presence of 5 mol% of the Rh^I catalyst.

thoxylbenzyl)maleimide (**1g**) in a highly enantiocontrolled manner (89–97% *ee*) to generate the corresponding *N*-PMB[15]-protected 3-arylsuccinimides in excellent yields (90–99%, entries 8–14). Maleimide **1h**, harboring an *N*-phenylethyl substituent, was also compatible in the transformation with variously substituted arylboronic acids, producing the desired products in chemical yields ranging from 90 to 99% and in 90 to 98% *ee* (entries 15–21).

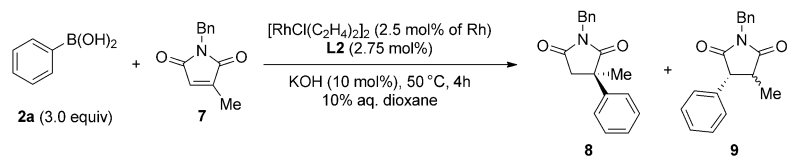
Finally, to demonstrate the synthetic utility of the asymmetric transformation, two compounds of pharmacological interest were targeted. Enantioselective addition of 2-methoxyphenylboronic acid (**2r**) to maleimide **1i** allowed the isolation of **3ir** in quantitative yield with 92% *ee* (Table 4, entry 22), which upon hydride reduction with $LiAlH_4$ (LAH) furnished pyrrolidine **4**, which is known to have high affinity for α-2 adrenoceptor subtypes, in 63% yield without the loss of selectivity (Scheme 1).[7a,16] Similarly, succinimide **3ao** which was prepared in Table 4, entry 7, was further reduced to yield (*R*)-*N*-benzyl-3-(2-trifluoromethyl)-phenylpyrrolidine (**5**), which is an intermediate, though with opposite configuration, in the synthesis of HSD-1 inhibitor **6**.[17]

After demonstrating the enantioselective arylation of maleimides, the Rh^I-catalyzed conjugate addition reaction of $PhB(OH)_2$ (**2a**) with substituted maleimides was tested (Table 5).[7c] Under the optimized conditions, the asymmetric addition of **2a** to *N*-benzyl-3-methylmaleimide (**7**) was complete in 4 h providing the addition products in a combined 97% yield. The addition occurred regioselectively to the less-hindered β-position giving compound **9** as the favored product (**8**/**9** = 19:81) with a 1:1.6 ratio of the *cis*/*trans* isomers. The addition products were generated with high enantioenrichment; compound **8**, the minor component with a quaternary stereogenic center was obtained



Scheme 1. Syntheses of known chiral 3-arylpyrrolidines.

Table 5. Asymmetric conjugate addition of $PhB(OH)_2$ (**2a**) to 3-methyl maleimide **7**.[a]



Entry	Yield [%][b]	**8**/**9**[c] (*cis*/*trans*)[c]	*ee* [%] of **8**[d]	*ee* [%] of *trans*-**9**[d]	*ee* [%] of *cis*-**9**[d]
1	97	19/81 (1:1.6)	96	92	96

[a] The reaction was carried out in dioxane (2.0 mL) at 50 °C for 4 h using maleimides **7** (0.2 mmol) and phenylboronic acids **2a** (0.6 mmol, 3.0 equiv based on **1**) in the presence of the rhodium catalyst generated in situ from $[RhCl(C_2H_4)_2]_2$ (2.5 μmol, 2.5 mol% of Rh) and chiral diene **L2** (5.5 μmol, 2.75 mol%). [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopic analysis of the crude mixture. [d] Determined by HPLC analysis using a chiral column (Chiralpak OJ).

with 96% *ee* whereas *trans*- and *cis*-**9** were produced with 92 and 96% *ee*, respectively.

Conclusion

In summary, the highly enantioselective 1,4-addition of a diverse range of arylboronic acids to *N*-substituted maleimides has been achieved using rhodium catalysts generated in situ from a family of novel 2,5-diaryl substituted bicyclo[2.2.1] chiral diene ligands. The reaction is generally rapid (2–6 h) and can be conducted under mild conditions (50 °C) in a range of solvents, preferably dioxane for synthetic or discovery chemistry applications, in the presence of carbonate or hydroxide bases and, preferably, ligand **L2**. For the scale-up of intermediates for pharmaceutical purposes in which dioxane should be avoided, it has been shown that other, less toxic, solvents can be used in its place. The asymmetric reaction is equally efficient for maleimides **1a**, **1g**, and **1i** bearing *N*-protecting groups, thereby representing a general method for the preparation of medicinally and synthetically useful 3-substituted succinimides with high optical purity (up to 98% *ee*). The synthetic method was applied to the concise preparation of chiral 3-arylpyrrolidines **4**, a biologically active compound, and **5**, the enantiomer of an intermediate in the synthesis of the HSD-1 inhibitor, compound **6**. The enantioselective conjugate addition of phenylboronic acid (**2a**) to the 3-methyl-substituted maleimide **7** gave addition products with moderate regioselectivity (**8**/**9** = 19:81) but with high enantioselectivity.

Experimental Section

General

All commercial chemicals and solvents were reagent grade and were used without further treatment unless otherwise noted. All reactions were carried out under an argon atmosphere. Reactions were monitored by TLC analysis using silica gel plates; zones were detected visually under ultraviolet irradiation (254 nm) or by spraying with 2,4-dinitrophenylhydrazine solutionfollowed by heating. Flash column chromatography was conducted using silica gel. ^1H NMR spectra were obtained on a 400 or a 500 MHz spectrometer. ^{13}C NMR spectra were obtained on a 100 or a 125 MHz spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) and were reported relative to the solvent peak. HRMS were obtained using EI, ESI, or FAB ionization methods. Optical purities of the final compounds were determined using chiral HPLC. Optical rotations were measured on a polarimeter. Melting points were measured on a melting points apparatus. Arylboronic acids and chiral dienes L11 and L12 are purchased from commercial sources and are used as received. Chiral bicyclo[2.2.1]diene ligands (L1–L10)[13b] and imides[18] were prepared according to the reported procedures.

General procedure for rhodium-catalyzed conjugate addition reactions

A solution of $[RhCl(C_2H_4)_2]_2$ (2.5 μmol, 2.5 mol% of Rh) and the selected chiral diene (5.5 μmol, 2.75 mol%) in 1,4-dioxane (1.0 mL) was stirred for 10 min at room temperature before adding KOH (0.1 M, 0.2 mL, 20 μmol) and the resulting solution was stirred for an additional 10 min at room temperature. After addition of $PhB(OH)_2$ (**2a**; 0.6 mmol) and stirring for 5 min, the mixture was transferred to a solution of maleimide **1a** (0.2 mmol) in 1,4-dioxane (1.0 mL). After having been stirred for 3 h at 50 °C, the mixture was filtered through a pad of silica gel and washed with Et_2O (10 mL × 3), and the volatiles were removed under reduced pressure to give the crude product, which was then purified by column chromatography using EtOAc/hexane (1:9) as eluent to afford the desired product **3aa**.

(*R*)-1-Benzyl-3-phenylpyrrolidine-2,5-dione (3aa)

Yield: 49.9 mg, 94%; M.p. 61–62 °C; *ee* was determined on a Daicel Chiralpak OD-H column eluting with hexane/isopropanol = 90:10, flow = 1 mL min^{-1}; retention times: 27.63 ((*S*)-enantiomer), 34.48 min ((*R*)-enantiomer). 96% *ee*; $[\alpha]_D^{22}$: −64.0 (*c* = 1.00 in $CHCl_3$). FTIR (KBr neat): $\tilde{\nu}$ = 3031, 1702, 1395, 1343, 1164, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.37 (m, 2H), 7.37–7.22 (m, 6H), 7.21–7.09 (m, 2H), 4.75 (d, *J* = 14.4 Hz, 1H), 4.69 (d, *J* = 14.4 Hz, 1H), 4.00 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.18 (dd, *J* = 18.4, 9.2 Hz, 1H), 2.81 ppm (dd, *J* = 18.4, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 175.7, 137.1, 135.7, 129.1, 128.8, 128.6, 128.0, 127.9, 127.3, 45.8, 42.7, 37.1 ppm. HRMS (EI): *m*/*z* calcd for $[C_{17}H_{15}NO_2]^+$ 265.1103; found: 265.1098 $[M]^+$.

General procedure for the syntheses of chiral 3-arylpyrrolidines

A mixture of compound **3ir** (50 mg, 0.14 mmol, 92% *ee*) and $LiAlH_4$ (29 mg, 0.76 mmol) in THF (2.5 mL) was stirred for 24 h at room temperature. The reaction was quenched with aqueous NaOH solution (10%, 0.15 mL) and H_2O, and the precipitate was filtered off through Celite and washed with EtOAc (10 mL × 3). The solvent was removed under reduced pressure, and the residue was purified on a silica gel column eluting with EtOAc/hexane = 1:1 to afford pyrrolidine **4** as a colorless oil.

(*R*)-1-[(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl]-3-(2-methoxyphenyl)pyrrolidine (4)

Yield: 28.7 mg, 63%; $[\alpha]_D^{27} = -16.05$ ($c = 1.19$ in $CHCl_3$); FTIR (KBr neat): $\tilde{\nu} = 3029, 1590, 1507, 1461, 1432, 1289, 1241, 1068, 919, 887, 815, 754\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$ (dd, $J = 7.6$, 1.6 Hz, 1H), 7.20–7.13 (m, 1H), 6.96–6.87 (m, 2H), 6.86–6.77 (m, 3H), 4.24 (s, 4H), 3.80 (s, 3H), 3.76–3.71 (m, 1H), 3.58 (s, 2H), 2.99 (t, $J = 8.8$ Hz, 1H), 2.83–2.76 (m, 1H), 2.73–2.63 (m, 1H), 2.55–2.46 (m, 1H), 2.34–2.22 (m, 1H), 1.92–1.80 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.1, 143.2, 142.4, 133.5, 132.7, 127.4, 126.9, 121.8, 120.6, 117.6, 116.8, 110.4, 64.3, 60.5, 60.0, 55.3, 54.4, 36.4, 31.8$ ppm; HRMS (FAB): *m/z* calcd for $[C_{20}H_{23}NO_3 + H]^+$ 326.1756; found: 326.1757 $[M+H]^+$.

(*R*)-1-Benzyl-3-[2-(trifluoromethyl)phenyl]pyrrolidine (5)

Yield: 27.5 mg, 60%; *ee* was determined on a Daicel Chiralpak AD-H column eluting with hexane/isopropanol = 99:1, flow = 0.1 mL min^{-1}; retention times: 64.05 ((*R*)-enantiomer), 69.84 min ((*S*)-enantiomer); 96.5% *ee*; $[\alpha]_D^{23} = +18.79$ ($c = 1.00$ in $CHCl_3$); FTIR (KBr neat): $\tilde{\nu} = 2960, 2790, 1491, 1452, 1381, 1343, 1118, 1024, 756, 699\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.66$ (d, $J = 8.0$ Hz, 1H), 7.53–7.39 (m, 2H), 7.32–7.21 (m, 4H), 7.20–7.12 (m, 2H), 3.73–3.65 (m, 1H), 3.64 (d, $J = 12.8$ Hz, 1H), 3.56 (d, $J = 12.8$ Hz, 1H), 2.87–2.75 (m, 2H), 2.64–2.49 (m, 2H), 2.36–2.24 (m, 1H), 1.82–1.78 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 146.2, 139.3, 132.2, 128.75, 128.74, 128.3, 128.0$ (q, $J = 29.0$ Hz), 127.0, 125.7, 125.12 (q, $J = 6.0$ Hz), 124.6 (q, $J = 272.0$ Hz), 62.9, 60.4, 54.9, 38.2, 35.0 ppm; HRMS (FAB^+): *m/z*: calcd for $[C_{18}H_{18}F_3N + Na]^+$ 328.1289; found: 328.1289 $[M+Na]^+$.

Acknowledgements

Financial support from the Ministry of Science and Technology of Republic of China (100-2113-003-009-MY2, 102-2113-003-006-MY2) and the National Taiwan Normal University is gratefully acknowledged.

Keywords: chiral ligands · conjugate addition · enantioselectivity · pyrrolidine · rhodium

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Received: March 18, 2015
Published online on June 3, 2015