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Preparation of Chiral 3-Arylpyrrolidines via the Enantioselective 1,4-Addition of Arylboronic Acids to Fumaric Esters Catalyzed by Rh(I)/Chiral Diene Complexes

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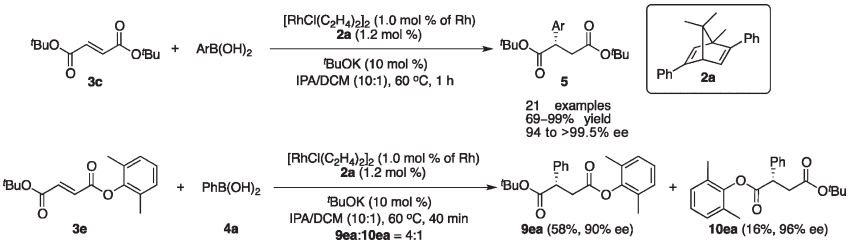
ABSTRACT



A highly efficient rhodium-catalyzed protocol for the preparation of 2-arylsuccinic esters and 3-arylpyrrolidines of high optical purity has been achieved. In the presence of 1 mol % of a chiral diene/Rh(I) catalyst, asymmetric addition of various arylboronic acids to di-*tert*-butyl fumarate (3c) provides the corresponding adducts in up to 99% yield and 94→99.5% ee. Excellent enantioselectivities were also observed in the regio- and enantioselective conjugate addition of phenylboronic acid (4a) to compound 3e.

Optically active 2-substituted succinic acid derivatives are valuable and important building blocks for the syntheses of various biologically active compounds and natural products.[1] Recently, chiral succinate derivatives bearing alkyl substituents have drawn much attention because they are potent inhibitors of matrix metalloproteases.[2] In the realm of synthetic transformation, the conjugate addition of organometallic reagents to electron-deficient olefins is one of the most powerful methods to efficiently construct a carbon–carbon bond.[3] Thus, in principle, stereoselective conjugate addition to 1,4-dicarbonyl but-2-enes is one of the possible methods that can generate chiral 2-substituted succinic esters efficiently. While Lewis acid mediated conjugate addition of alkyl radicals to fumarates possessing chiral auxiliaries has been found to proceed with high diastereoselectivity,[4] reports on the catalytic enantioselective conjugate addition reaction of organometallic reagents to 1,4-unsaturated dicarbonyl compounds are sparse.[5] In many recently developed rhodium-catalyzed asymmetric transformations, rhodium–chiral diene complexes have emerged as highly efficacious catalysts, possessing high

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catalytic activity and enantioselectivity, particularly in the asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds.[6] Compared with Michael acceptors such as α,β-unsaturated amides, aldehydes, and ketones, which all perform successfully in catalytic asymmetric Rh-catalyzed arylation reactions, fumaric or maleic acid derivatives are less reactive and have thus received far less attention. To the best of our knowledge, only one example of the enantioselective arylation of fumarate esters has been described, and it came from Hayashi's laboratory.[5a] A significant problem usually encountered in these systems is that conventional chiral phosphorus-based ligands are often ineffective in promoting the Rh-catalyzed asymmetric addition reaction of phenylboronic acid to fumarates. This is not the case with bulky, substituted diene ligand **1**, which is able to induce high enantioselectivity in this process (up to 90% ee) (Figure. 1).[5a] As part of our continuing efforts in the development of chiral 2,5-diaryl-substituted bicyclo[2.2.1] diene ligands that are stable, easy to prepare, and behave with high fidelity in enantioselective metal-catalyzed asymmetric transformations, diene ligands **2d** and **2h** were recently synthesized and found to be extremely effective chiral modifiers for the Rh-catalyzed conjugate addition of various arylboronic acids to acyclic and cyclic α,β-unsaturated carbonyl compounds, respectively.[7] It was entirely natural, therefore, that we should wish to extend our studies to the asymmetric 1,4-addition of arylboronic acids to fumarate and maleate esters to establish possible efficacy of diene ligands **2** in these notoriously difficult Michael acceptor systems.

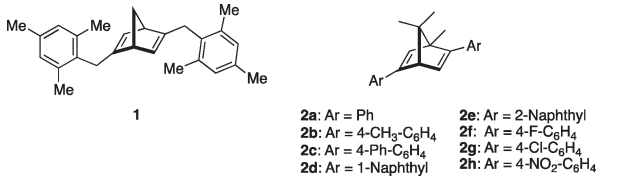
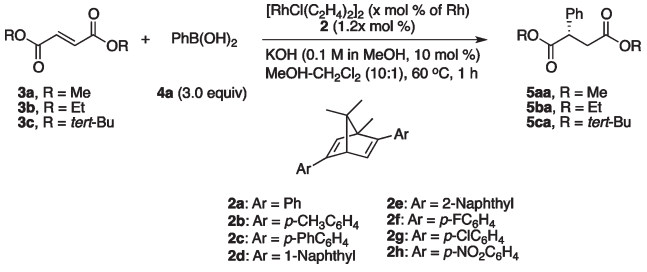


Figure 1. Chiral bicyclo[2.2.1] diene ligands.

Our studies commenced with identifying the ideal combination of fumarate ester functionality and chiral catalyst that could offer high selectivity in the conjugate addition reaction (Table 1). Initially, addition of phenylboronic acid (**4a**), in the presence of 5 mol % of Rh/**2a**, to dimethyl fumarate esters **3a** was studied in the cosolvent mixture of MeOH and CH_2Cl_2 (10:1). The catalytic reaction was complete within 1 h and afforded the desired product (**5aa**) in 89% yield but with poor enantioselectivity (34% ee) (entry 1). The enantioinduction could be enhanced to 77% ee and 99% ee in the case of diethyl (**3b**) and di-*tert*-butyl fumarates (**3c**), respectively (entries 2 and 3). High ee (98%) was also observed using di-*tert*-butyl maleate as a substrate (entry 4). Next, the effect of catalyst loading on the reaction with substrate **3c** was screened. In the presence of 1 mol % of the rhodium/**2a** complex, the reaction was found to produce 92% of adduct **5ca** with 97% ee, which was not that much different from when 3 mol % of the catalyst was used (entries 5 and 6). Subsequently, the effect of having different aryl substituents in the ligands was investigated with regard to reaction outcome. Ligands with *p*-methyl phenyl or *p*-biphenyl substituents were initially studied (ligands **2b** and **2c**, entries 7 and 8), followed by dienes with 1- and 2-naphthyl groups (ligands **2d** and **2e**, entries 9 and 10) or electron-withdrawing substituents at 4-position of benzenoid systems (ligands **2f**–**h**, entries 11–13). All of these gave rise to levels of enantioselectivity similar to those with ligand **2a** in the aforementioned process.

Table 1. Asymmetric Conjugate Addition of Phenylboronic Acid to Fumaric Esters[a]



entry	ligand	R	Rh (*x* mol %)	yield[b] (%)	ee[c] (%)
1	**2a**	Me	5.0	89	34
2	**2a**	Et	5.0	99	77
3	**2a**	^{t}Bu	5.0	99	99
4[d]	**2a**	^{t}Bu	5.0	83	98
5	**2a**	^{t}Bu	3.0	87	98
6	**2a**	^{t}Bu	1.0	92	97
7	**2b**	^{t}Bu	1.0	81	96
8	**2c**	^{t}Bu	1.0	99	95
9	**2d**	^{t}Bu	1.0	95	96
10	**2e**	^{t}Bu	1.0	99	97
11	**2f**	^{t}Bu	1.0	62	97
12	**2g**	^{t}Bu	1.0	96	97
13	**2h**	^{t}Bu	1.0	97	97

[a] The reaction was conducted with 1 mmol of substrate **3**. [b] Calibrated GC yield using *n*–decane as an internal standard. [c] Determined by chiral HPLC; see the Supporting Information. [d] Di-*tert*-butyl maleate was used, and (*S*)-**5ca** was obtained.

Because the structural effect of various ligands on the enantioselectivity was subtle, ligand **2a** was used for

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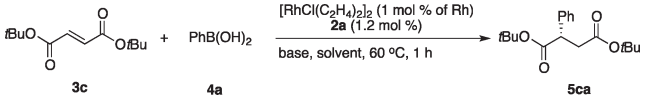
Table 2. Optimization of Reaction Conditions[a]



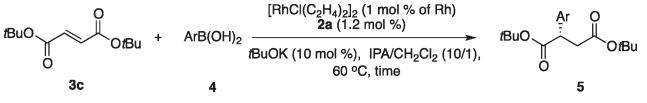
entry	solvent	base[b]	yield[c] (%)	ee[d] (%)
1	$MeOH/CH_2Cl_2$ (10:1)	KOH	92	97
2	$MeOH/(CH_2Cl)_2$ (10:1)	KOH	98	97
3	IPA/CH_2Cl_2 (10:1)	KOH	91	99
4	$IPA/(CH_2Cl)_2$ (10:1)	KOH	73	99
5	IPA/CH_2Cl_2 (10:1)	NaOH	94	99
6	IPA/CH_2Cl_2 (10:1)	LiOH	98	99
7	IPA/CH_2Cl_2 (10:1)	CsOH	93	98
8	IPA/CH_2Cl_2 (10:1)	EtONa	99	97
9	IPA/CH_2Cl_2 (10:1)	^{t}BuOK	99	99.5
10[e]	IPA/CH_2Cl_2 (10:1)	Et_3N[f]	93	97
11	IPA/CH_2Cl_2 (10:1)	DIPA[f]	62	97

[a] The reaction was conducted with 1 mmol of substrate **3c**. [b] 0.1 M in MeOH. [c] Calibrated GC yield using *n*-decane as an internal standard. [d] Determined by chiral HPLC; see the Supporting Information. [e] It was reacted at 60 °C. [f] Neat base was used.

optimization of the reaction parameters (Table 2). Initially, solvent effects were explored (entries 1−4). While a model reaction of the conjugate addition of phenylboronic acid (**4a**) to compound (**3c**) saw a slight improvement in chemical yield using a combination of methanol and ethylene dichloride (entry 2), better enantioselectivity was observed when the solvent mixture of 2-propanol and dichloromethane was used (entry 3).[8] Our study of the effect of different bases (entries 5−11) showed no prominent enhancement in yield or ee with different bases except when the reaction was conducted in the presence of 10 mol % of *t*-BuOK, which yielded compound **5ca** in >99% yield and 99.5% ee (entry 9).[9]

Subsequently, various substrates were investigated under the optimized reaction conditions specified in Table 2, entry 9, in order to explore the scope of the asymmetric reaction.[10] A handful of arylboronic acids were submitted to the reaction conditions at 60 °C, and the results are summarized in Table 3. The adducts (**5cb**−**ci**), from the conjugate reaction of different substituted arylboronic acids to compound **3c**, were isolated in excellent chemical yield and enantioselectivity (entries 2−9). When 1-naphthyl and 2-naphthylboronic acids were both tested, the Michael adducts **5cj** and **5ck** were isolated in comparable yields and stereoselectivity (entries 10 and 11). Notably, the use of arylboronic acids containing electron-withdrawing substituents exhibited a negligible effect on the reaction outcome (entries 12−21), except that a longer

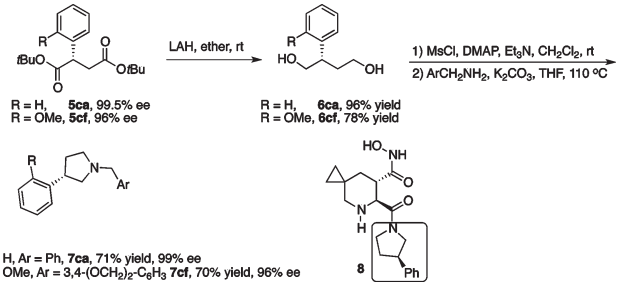
Table 3. Substrate Scope[a]



entry	Ar	time (h)	yield[b] (%)	ee[c] (%)
1	C_6H_5 (**4a**)	1	99 (**5ca**)	99.5
2	4-Ph-C_6H_4 (**4b**)	1	99 (**5cb**)	98
3	2-Me-C_6H_4 (**4c**)	1	99 (**5cc**)	98
4	3-Me-C_6H_4 (**4d**)	1	99 (**5cd**)	95
5	4-Me-C_6H_4 (**4e**)	1	99 (**5ce**)	96
6	2-MeO-C_6H_4 (**4f**)	1	99 (**5cf**)	96
7	3-MeO-C_6H_4 (**4g**)	1	99 (**5cg**)	95
8	4-MeO-C_6H_4 (**4h**)	1.3	99 (**5ch**)	96
9	4-^{t}Bu-C_6H_4 (**4i**)	1	99 (**5ci**)	95
10	1-naphthyl (**4j**)	1	99 (**5cj**)	97
11	2-naphthyl (**4k**)	1	99 (**5ck**)	94
12	3-Cl-C_6H_4 (**4l**)	1	99 (**5cl**)	97
13	4-Cl-C_6H_4 (**4m**)	1	82 (**5cm**)	98
14	4-F-C_6H_4 (**4n**)	1	99 (**5cn**)	99
15	2,5-F_2-C_6H_3 (**4o**)	1	77 (**5co**)	97
16	2-CF_3-C_6H_4 (**4p**)	28	85 (**5cp**)	>99.5
17	3-CF_3-C_6H_4 (**4q**)	1	99 (**5cq**)	97
18	4-CF_3-C_6H_4 (**4r**)	1	99 (**5cr**)	95
19	4-Ac-C_6H_4 (**4s**)	1	99 (**5cs**)	98
20	3-NO_2-C_6H_4 (**4t**)	1	99 (**5ct**)	96
21	4-NO_2-C_6H_4 (**4u**)	137	69 (**5cu**)	97

[a] The reaction was conducted with 1 mmol of substrate **3c**. [b] Isolated yield. [c] Determined by chiral HPLC; see the Supporting Information.

Scheme 1. Syntheses of Optially Active 3-Arylpyrrolidines



reaction time was required in the case of 2-CF_3 and 4-NO_2 substituted phenylboronic acids (entries 16 and 21).

The synthetic utility of this asymmetric conjugate addition was then extended to the synthesis of several different optically active *N*-substituted 3-arylpyrrolidines found in certain biologically active substances.[11,12] Thus, the

(8) The use of a single solvent such as, MeOH, ^{t}BuOH, dioxane, THF, or toluene provides the desire adduct with comparable ee but in less chemical yield than utilizing a mixture of IPA and DCM.

(9) The optimal reaction condition was applied to the catalytic reaction of compound **3c** with compound **4a** in the presence of 0.5 mol % of Rh/**2a**, providing the adduct **5ca** with 21% yield and 98% ee after 17 h.

(10) The configurations of the adducts were determined by comparing the sign of the specific rotation with those of the reported samples in the literature.

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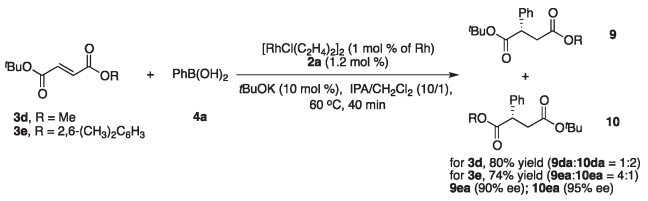
Michael adduct **5ca** was reduced by LAH to provide the corresponding diol **6ca** in 96% yield,[5a,13] which was subjected to mesylation and *N*,*N*-dialkylation with benzylamine to yield compound **7ca** in 71% yield and 99% ee; this is a synthetic precursor of compound **8**, a potent inhibitor of ADAM-10 and HER-2.[11,14] Similarly, compound **5cf** underwent reduction, mesylation, and *N*,*N*-dialkylation with 2,3-dihydro-1,4-benzodioxin-6-ylmethylamine to provide the biologically active compound **7cf**, an enantiomer of the α-2-adrenocepter antagonist developed by Novartis (Scheme 1).[12]

Scheme 2. Enantioselective Conjugate Addition of Phenylboronic Acid to Fumarates of Two Distinct Esters



Having achieved the catalytic asymmetric addition of an array of arylboronic acids to di-*tert*-butyl fumarate (**3c**) in excellent enantioselectivity and yield, the catalytic asymmetric conjugate addition of phenylboronic acid to fumarates bearing two distinct ester functional groups was carried out (Scheme 2). Under the optimal reaction conditions, addition of phenylboronic acid (**4a**) to *tert*-butyl methyl fumarate (**3d**) furnished the desired yet inseparable mixture of regioisomeric adducts **9da** and **10da** in a ratio of 1:2 with overall 80% yield.[15,16] While the level of regiocontrol observed in this reaction was unimpressive, it was slightly enhanced when substrate **3e** was tested, yielding adducts **9ea** and **10ea** in an overall yield of 74% with 90% and 95% ee, respectively.[17] The bulkier 2,6-dimethylphenyl ester accounts for the formation of compound **9ea** as the major regioisomer.

In conclusion, we have successfully devised a protocol for the synthesis of optically active 3-arylsuccinates via the Rh-catalyzed conjugate addition of various arylboronic acids to di-*tert*-butyl fumarate (**3c**). This catalytic asymmetric conjugate addition procures the Michael adducts (**5ca**−**cu**) in excellent yield and enantioselectivity. The synthetic applicability of this method was also expanded to encompass the syntheses of chiral 3-arylpyrrolidine derivatives (**7ca**, **7cf**). Moreover, our catalytic system has been utilized for the first study of the regio- and enantioselective conjugate addition of phenylboronic acid (**4a**) to fumarates possessing two distinct esters, providing a new route for the preparation of differently protected fumarates in a highly enantioselective manner. From these results, fumarates were successfully added to a growing chain of Michael acceptor substrates in the process of highly enantioselective Rh-catalyzed 1,4-addition of arylboronic acids. Further investigations on other poorly performing Michael acceptor systems are currently under intensive investigation in this group, and the results will be reported in due course.

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

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(14) Roussi, G.; Zhang, J. *Tetrahedron* **1991**, *47*, 5161.

(15) The regioselectivity was determined by ^{1}H NMR spectra of the reaction mixture based on the authentic compounds synthesized from the alkylation reaction of enolates derived from 2-phenyl acetates, see Supporting Information.

(16) The inseparable diastereomeric mixture, **9da** and **10da**, on both normal column chromatography and HPLC complicate the determination of ee values.

(17) The absolute configurations of **9ea** and **1oea** were determined by comparing the sign of the specific rotation with those prepared from Evan's oxazolidinone chemistry; see the Supporting Information.

The authors declare no competing financial interest.