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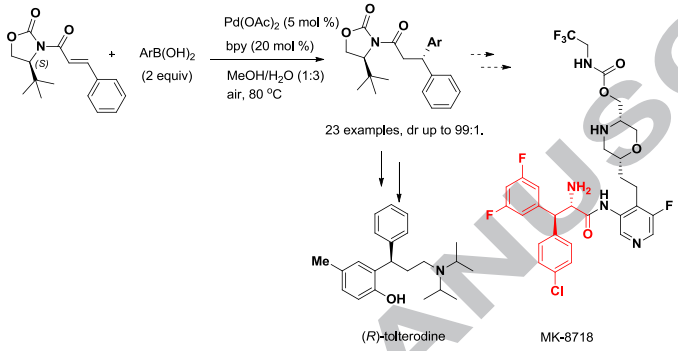

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Palladium-Catalyzed Diastereoselective Synthesis of β, β-Diarylpropionic Acid Derivatives and Its Application to the Total Synthesis of (R)-Tolterodine and the Enantiomer of a key Intermediate for MK-8718

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ABSTRACT

Palladium-catalyzed diastereoselective synthesis of optically active β, β-diarylpropionic acid derivatives employing 4-(tert-butyl)oxazolidin-2-one as the chiral auxiliary under an air atmosphere in excellent yields with high diastereoselectivity is reported. The catalytic system is applied to the total synthesis of (*R*)-tolterodine and the enantiomer of a key intermediate for MK-8718.

Introduction

Chiral β, β-diaryl-substitued compounds are important structural moieties that are found in many pharmaceuticals (e.g., tolterodine,[1] sertraline[2]), bioactive compounds (e.g., MK-8718[3]) and natural products (e.g., podophyllotoxin,[4] cherylline[5]). Due to their diverse biological properties such as antioxidant activity, bacteriostatic, growth modulation, disease prevention and antitumor properties, the enantioselective construction of stereogenic carbon centers substituted with two aryl groups has become an attractive subject.

Thus far, many methods for accessing chiral β, β-diarylpropionic acids have been reported, such as cuprum[6]-, cobalt[7]-, or rhodium[8]- catalyzed asymmetric 1,4-reduction of β, β-diaryl-substitued unsaturated acrylates or nitriles using hydrosilane or borohydride as the reductants, and direct enantioselective hydrogenation of β,β-diaryl-substitued unsaturated acrylic acids or acrylates with molecular H_2.[9] Among these, asymmetric 1, 4-addition of nucleophilic reagents to α, β-unsaturated carbonyl compounds catalyzed by Pd, Rh, or Cu complexes is a more popular and practical method.[10]

Recently, we have explored the palladium-catalyzed diastereoselective conjugate addition of arylboronic acids to chiral imides as a convenient method to obtain optically active 3-arylbutanoic acids.[11] Herein, we report the method for palladium-catalyzed diastereoselective synthesis of optically active β, β-diarylpropionic acids and its application to the total synthesis of (R)-tolterodine[1, 12] and the enantiomer of a key intermediate for MK-8718.[3] (R)-tolterodine, an important urological drug used in the treatment of urinary incontinence. MK-8718, a novel HIV protease inhibitor with a favorable pharmacokinetic profile with potential for further development, is discovered by Merck research laboratory.

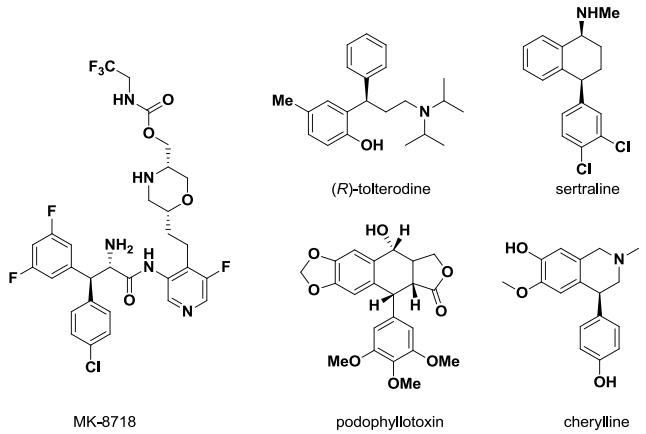

Figure 1. Chiral β, β-diaryl-substituted pharmaceuticals, bioactive compounds, and natural products

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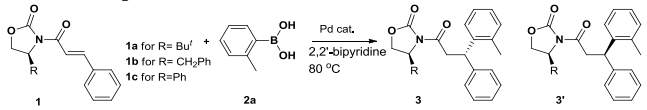
Results and Discussion

Evans-oxazolidinones[13] have been used as chiral auxiliaries in many stereoselective transformations and applied to synthesis of varies of nature products and bioactive compounds. At first, three Evans-oxazolidinones were used as the chiral auxiliaries (entries 1-3), (S)-4-tert-butyloxazolidin-2-one, (S)-4-benzyloxazolidin-2-one (**a**), and (S)-4-phenyloxazolidin-2-one, were installed on cinnamoyl chloride to give the corresponding cinnamamides (**1a−c**). As shown in Table 1, (S)-4-tert-butyloxazolidin-2-one was found to be a more efficient chiral auxiliary for the diastereoselective conjugate addition of o-tolylboronic acid to imide, using $Pd(OAc)_2$ as the catalyst and 2,2'-bipyridine as the ligand in mixed solvent of MeOH/H_2O (1:3) at 80 °C. And **3a** with *S*-configuration could be easily isolated by column chromatography on silica gel using petroleum ether/ethyl acetate as the eluent. And the higher conversion was due to **1a**'s better solubility in the mixed solvent.

Table 1. Optimization of the Reaction Conditions[a]



entry	**1**	catalyst	solvent	Conv (%)[b]	dr[c](**3**/**3'**)
1	**1a**	$Pd(OAc)_2$	MeOH/H_2O(1:3)	>99	15:1
2	**1b**	$Pd(OAc)_2$	MeOH/H_2O(1:3)	62	6:1
3	**1c**	$Pd(OAc)_2$	MeOH/H_2O(1:3)	81	3:1
4	**1a**	$Pd(OAc)_2$	MeOH	>99	6:1
5	**1a**	$Pd(OAc)_2$	MeOH/H_2O(1:1)	>99	11:1
6	**1a**	$Pd(OAc)_2$	MeOH/H_2O(1:5)	75	10:1
7	**1a**	$Pd(OAc)_2$	H_2O	65	6:1
8	**1a**	$PdCl_2$	MeOH/H_2O(1:1)	>99	11:1
9	**1a**	$PdCl_2$	MeOH/H_2O(1:3)	>99	15:1
10	**1a**	$Pd(OAc)_2$	HOAc/THF/ H_2O(1:2:0.6)	NR	
11	**1a**	$Pd(OAc)_2$	Acetone/H_2O(1:1)	>99	9:1
12[d]	**1a**	$Pd(OAc)_2$	MeOH/H_2O(1:3)	70	15:1

[a]Reaction conditions: under an air atmosphere, chiral imide (0.5 mmol), o-tolylboronic acid (**2**) (1 mmol), catalyst (0.025 mmol), 2,2'-bipyridine (0.1 mmol), solvent (4 mL), time (12 h), in a sealed Schlenk tube at 80 °C.

[b]Determined by ^{1}H NMR analysis of the crude reaction mixture.

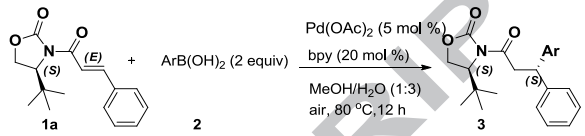
[c]The diastereoselective ratio (dr value) was determined according to the ^{1}H NMR peak areas of α-H in **3** and **3'** from the reaction mixture of **1** with **2a**.

[d]2,2'-bipyridine (0.05 mmol) was used, and reacted for 24 h.

Conjugate addition and oxidative Heck reaction are competitive, the application of appropriate solvent have been proved to be important for the palladium-catalyzed 1, 4-addition of nucleophilic reagents to α, β-unsaturated carbonyl compounds.[14] Firstly, the effect of different rations of methanol and water was investigated, higher diastereoselective ratio of **3**/**3'** (dr. value up to 15:1) without oxidative Heck product was obtained in case of the mixed solvent of MeOH/H_2O (1:3) was used (entry 1). When the proportion of MeOH/H_2O was reduced, the conjugate addition products were found to be major products together with lower than 5% oxidative Heck product with lower diastereoselective ratio of **3**/**3'** (entries 4-7). Other solvents were also investigated. Only trace product was found when the acidic solvent of HOAc/THF/H_2O was used (entry 10), which worked well in Lin's work.[14a, 14e] 3% Oxidative Heck product was also found in the mixture of acetone/H_2O (1:1) with moderate *dr*. value (entry 11). The results indicated that solvents played an important role in this diastereoselective conjugate addition of arylboronic acid to cinnamamide with chiral auxiliaries.

$PdCl_2$ showed a similar activity compared to $Pd(OAc)_2$ in the mixture solvent of methanol and water (entry 8-9). When the loading of 2,2'-bipyridine was reduced to 0.1 equiv, the conversion decreased to 70% even if the reaction proceeded for 24 h (entry 12).

Table 2. Palladium-catalyzed conjugate addition of arylboronic acids to chiral Imide[a]



entry	Ar	Conv.(%)[b]	dr[c]	Yield(%)[d]
1	*o*-MeC_6H_4	>99	93:7(NMR)	**3a** 89
2	*m*-MeC_6H_4	>99	99:1	**3b** 92
3	*p*-MeC_6H_4	>99	99:1	**3c** 93
4	*o*-$CF_3C_6H_4$	0	-	-
5[e]	*m*-$CF_3C_6H_4$	95	99:1	**3d** 91
6[e]	*p*-$CF_3C_6H_4$	93	96:4	**3e** 89
7[e]	*o*-ClC_6H_4	85	90:10	**3f** -62
8	*m*-ClC_6H_4	>99	99:1	**3g** 94
9	*p*-ClC_6H_4	>99	99:1	**3h** 92
10[e]	*m*-CNC_6H_4	95	92:8	**3i** 85
11[e]	*p*-CNC_6H_4	98	96:4	**3j** 87
12	*o*-$MeOC_6H_4$	>99	98:2	**3k** 92
13	*m*-$MeOC_6H_4$	>99	93:7	**3l** 86
14[e]	*p*-$NH_2COC_6H_4$	98	96:4	**3m** 88
15	*p*-$OHCH_2C_6H_4$	98	99:1	**3n** 93
16[e]	*p*-$CHOC_6H_4$	98	95:5	**3o** 86
17	*m*-$MeCOC_6H_4$	>99	95:5	**3p** 85
18	*p*-HOC_6H_4	>99	94:6	**3q** 82
19	3,4-difuoro C_6H_3	96	93:7	**3r** 84
20	3,4-MeO C_6H_3	>99	99:1	**3s** 95
21	3-thioenyl	>99	98:2	**3t** 95
22[e]	2-furanyl	83	99:1	**3u** 80
23	2-phenyl	0	-	-

[a]Reaction conditions: under an air atmosphere, chiral imide (**1a**) (0.5 mmol), arylboronic acid (**2**) (1 mmol), $Pd(OAc)_2$ (0.025 mmol), 2,2'-bipyridine (0.1 mmol), MeOH (1 mL), H_2O (3 mL), time (12 h), in a sealed Schlenk tube at 80 °C.

[b]Determined by ^{1}H NMR analysis of the crude reaction mixture.

[c]The diastereoselective ratio (dr value) was determined according to HPLC of the reaction mixture of **1a** with **2**.

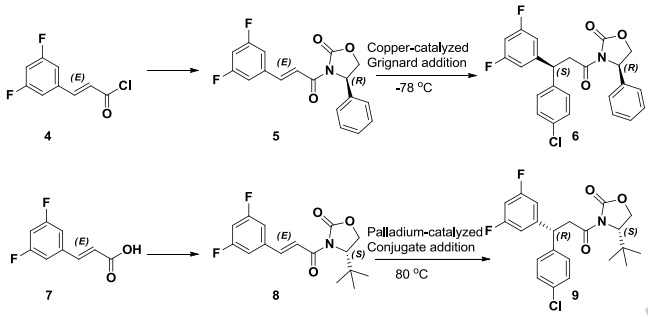
[d]Isolated yield.

[e]Reacted for 24 h

As illustrated in Table 2, the present diastereoselective conjugate additions of a broad range of arylboronic acids were evaluated for reaction with **1a** under the standard conditions. The conjugate addition proceeded in high yields (up to 95%) with excellent diastereoselectivity (dr. value up to 99:1) for most of the substrate combinations. Arylboronic acids substituted with diverse functional groups such as methyl, methoxyl, trifluoromethyl, amide, halogen, ester, ketone, aldehyde, hydroxyl and methylol at the ortho-, meta-, and para-positions on the phenyl were tolerated under the optimal conditions, except for (2-(trifluoromethyl)phenyl)-

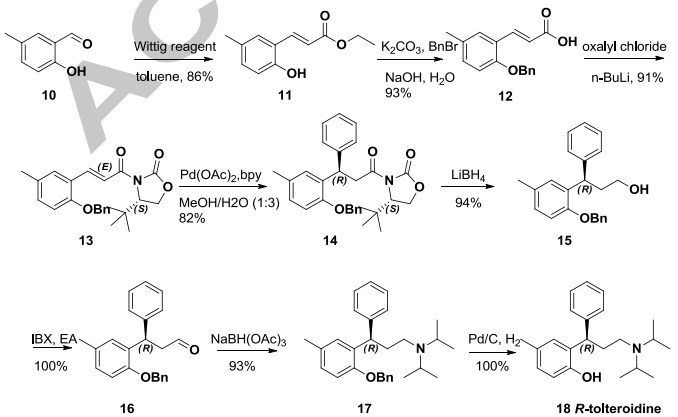
boronic acid (entry 4) and [1,1'-biphenyl]-2-ylboronic acid (entry 23) which was due to the bigger steric substituents in the *ortho*-position. Arylboronic acids with electron-withdrawing substituents need longer time to give high conversion (entries 5, 6, 10, 11, 14, 16). (2-Chlorophenyl)boronic acid also gave low conversion (entry 7). The reaction worked well for hetero-arylboronic acids, such as furan-2-ylboronic acid, thiophen-3-ylboronic acid (entry 21 and 22). Therefore, the present method could easily afford diverse chiral β, β-diarylpropionic acid derivatives.

In addition, a single crystal of **3j** was prepared to further confirm the absolute configuration, and its structure was unambiguously confirmed by X-ray diffraction analysis. The X-ray diffraction analysis indicated that the conjugate addition intends to form the product with the *S*-configuration.[16]



Scheme 1. Synthesis of the enantiomer of a key intermediate **6** for MK-8718.

As shown in scheme 1, cryloyloxazolidinone **6** was a key intermediate for synthesis of MK-8718, obtained by copper-catalyzed Grignard addition at -78 °C in Bungard's work,[3] low temperature restricted the large scale application of this method. Our present palladium-catalyzed diastereoselective addition was applied to synthesis of the similar cryloyloxazolidinone **9** on a gram scale, which was the enantiomer of a key intermediate for MK-8718. Firstly, compound **7** reacted with oxalyl chloride to give (E)-3-(3, 5-difluorophenyl)acryloyl chloride, then treated with (S)-4-tert-butyloxazolidin-2-one to afford the desired acrylooxazolidinone **8**. Secondly, the diastereoselective conjugate addition of (4-chlorophenyl)boronic acid to acrylooxazolidinone **8** was performed under the optimized conditions to give cryloyloxazolidinone **9** in high yields (76% over 2 steps).



Scheme 2 Total Synthesis of (*R*)-tolterodine.

Then, the present palladium-catalyzed diastereoselective conjugate addition of arylboronic acids to chiral imides was applied to the total synthesis of (*R*)-tolterodine on a gram scale.[1, 12] Different approaches have been reported for the racemic and asymmetric synthesis of tolterodine over the last decades.

Scheme 2 illustrated the reaction scheme that involved. The synthesis commenced with Wittig reaction of couple commercially available 2-hydroxy-5-methyl-benzaldehyde **10** and ethyl 2-(triphenylphosphoranylidene)acetate, afforded the corresponding cinnamate ester **11**. A sequence of benzylation, hydrolysis of **11** gave compound **12** with good overall efficiency. Then compound **12** was treated with oxalyl chloride to give corresponding cinnamoyl chloride, which reacted with (S)-4-tert-butyloxazolidin-2-one to form the key intermediate cinnamamide **13**. As a key step, the diastereoselective conjugate addition of phenylboronic acid to cinnamamide **13** under our optimized conditions furnished the diaryl derivative **14** in 82% yield, and the dr value of which was determined as **14: 14'** = 90: 10 by analysis of ^{1}H NMR of the crude products. Reduction of compound **14** by treatment with $LiBH_4$ in Et_2O at 0 °C gave 94% yield of alcohol **15**. The hydroxyl group in alcohol **15** was successfully oxidated to corresponding aldehyde, and subsequent reductive amination with diisopropylamine and sodium triacetoxyborohydride gave the protected tolterodine precursor in high yields. Deprotection of benzyl applying hydrogenolysis gave (*R*)-tolterodine in high yield.

The R configuration was confirmed by comparison of the optical rotations with that reported for (S)-tolterodine[15] {$[\alpha]^{20}_D$ -23.0 (c 1.5, MeOH)}. Thus, using our new method in the key step, (*R*)-tolterodine was synthesized through an eight-step sequence from 2-hydroxy-5-methyl-benzaldehyde **10** in an overall yield of 52%.

Conclusion

In summary, we have developed a convenient, efficient and practical palladium-catalyzed method for the diastereoselective synthesis of optically active chiral β, β-diarylpropionic acid derivatives. The protocol relies on the use of easily available substrates, cheap ligands and recoverable chiral auxiliary groups. The notable advantage of this method is that it is simple and compatible with a variety of functional groups (halide, cyano, ester, amide, methylol, etc.). Moreover, the desired optically active 3-arylbutanoic acid derivatives could be obtained in excellent yields with a high diastereoselectivity. Therefore, the present method provides a novel and valuable strategy for the synthesis of diverse optically active 3-arylbutanoic acid derivatives. Furthermore, this methodology is applied to the total synthesis of (*R*)-tolterodine and the enantiomer of a key intermediate for MK-8718.

Acknowledgments

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16. Crystallographic data for the structure has been deposited with the Cambridge Crystallographic Data Centre (CCDC 1573302). See the Supporting Information for details. The absolute configuration of other products was tentatively assigned by analogy.

Highlights

• Palladium-catalyzed diastereoselective synthesis of optically active chiral β, β-diarylpropionic acid derivatives.
• With excellent yields and high diastereoselectivity.
• This catalytic system was applied to the total synthesis of (R)-tolterodine.
• This catalytic system was performed on gram-scale.