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Mechanistic switch leading to highly efficient chirality transfer in Pd(0)-catalyzed coupling–cyclization of aryl iodides with 1:1 acid–base salts of 2,3-allenoic acids and L-(−)-cinchonidine or D-(+)-/L-(−)-α-methylbenzylamine. Enantioselective synthesis of highly optically active 3-aryl polysubstituted butenolides†

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An efficient methodology provides an easy access to highly optically active polysubstituted butenolides starting from aryl halides and 1:1 salts of optically active 2,3-allenoic acid–base *via* an oxidative addition–coordinative cyclization–reductive elimination mechanism, which led to the high efficiency of this chirality isomerization reaction.

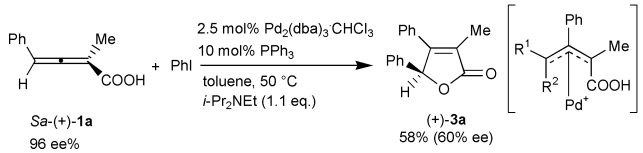
Chirality transfer processes involving the disappearance of an original chirality and the establishment of a new chirality is one of the best ways to obtain optically active compounds from the easily available optically active starting materials provided that the chirality can be 'remembered' in the corresponding transition state(s) or intermediate(s) therein. In this paper, we wish to report an efficient chirality transfer process, *i.e.*, the Pd(0)-catalyzed coupling–cyclization of aryl iodides with 1:1 acid–base salts of 2,3-allenoic acids and L-(−)-cinchonidine or D-(+)-/L-(−)-α-methylbenzylamine, which provides an efficient entry to highly optically active 3-aryl polysubstituted butenolides.

Highly optically active polysubstituted butenolides are a class of important compounds with potential biological activities,[1,2] but the synthesis of these compounds has rarely been reported.[3] Recently, among our efforts devoted towards the synthesis of heterocyclic compounds from functionalized allenes,[4] we have established a Pd(0)/Ag^+-cocatalyzed coupling–cyclization reaction of organic halides with 2,3-allenoic acids to afford racemic polysubstituted butenolides.[5]

It occurred to us that it would be possible to synthesize optically active butenolides with high ee value starting from 2,3-allenoic acids with high enantiopurity and organic halides. The most formidable challenge in this reaction is the chirality transfer ability of the possible intermediates from the chiral allenoic acids.

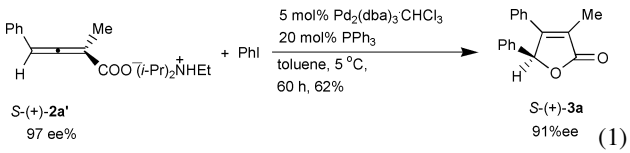
The reaction of *Sa*-(+)-**1a**[6–8] with PhI under the catalysis of Pd(0) was studied (Scheme 1). The results are somewhat disappointing as well as encouraging since the highest ee of (+)-**3a**[9] observed was 60% indicating that the π-allyl palladium species[5] did partially 'remember' the chirality in 2,3-allenoic acids (Scheme 1).

In order to increase the efficiency of chirality transfer, we reasoned that if we could make the mechanistic switch from a π-allyl palladium mechanism[5] to an oxidative addition–coordinative cyclization–reductive elimination mechanism (Scheme 2), the chirality of allene moiety can be transferred into the chiral center in butenolides highly efficiently.



Scheme 1

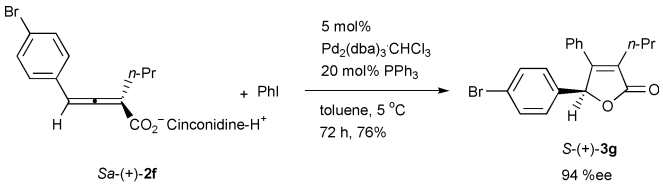
Thus, the 1:1 salt *Sa*-(+)-**2a′** was prepared from *Sa*-(+)-**1a** and $(i\text{-Pr})_2$NEt and its Pd(0)-catalyzed reaction with PhI afforded *S*-(+)-**3a** in 62% yield and 91% ee (eqn. 1)!



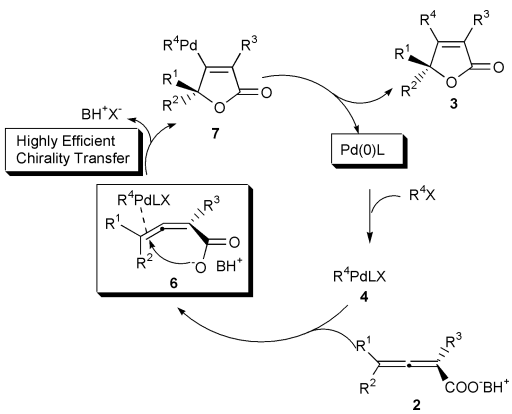
(1)

Furthermore, when the 1:1 acid–base salt *Sa*-(+)-**2a** was used *directly* instead of *Sa*-(+)-**1a** as the starting material, the reaction afforded *S*-(+)-**3a** in 95% yield and a remarkable 87% ee at rt! No reaction was observed in the absence of TBAB probably due to the low solubility of *Sa*-(+)-**2a** in toluene. It was observed that the reaction temperature was important. When the reaction was carried out at 5 °C, *S*-(+)-**3a** was isolated in 90% yield and 91% ee (entry 1, Table 1), while at a higher temperature, both the yields and ee were considerably lower.

In order to study the detail of this chirality transfer process, we synthesized 2-(*n*-propyl)-4-(4′-bromophenyl)-2,3-butadienoic acid **1f** and its corresponding L-(−)-cinchonidine salt *Sa*-(+)-**2f**. The corresponding reaction under the comparable reaction conditions afforded S-(+)-**3g** (eqn. 2).



(2)



Scheme 2

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b1/b109645a/

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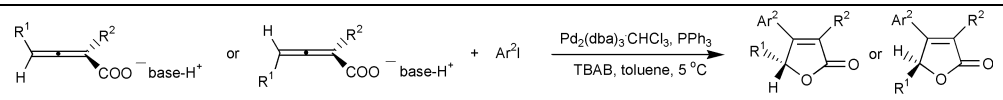
Table 1 Enantioselective synthesis of 3-aryl butenolides *via* the Pd(0)-catalyzed coupling–cyclization reaction of 1 : 1 acid–base salts of 2,3-allenoic acids and chiral bases[a]



2 2 3 3

	1 : 1 salt							
Entry	R^1	R^2	Base	acid–base Salt[b,c]	Ar^2I	Time (h)	Yield[g] (%)	ee (%)[d]
1	Ph	Me	A	(+)-**2a** (97% ee)	Ph	48	90 (*S*-(+)-**3a**)	91
2	Ph	Me	A	(+)-**2a** (97% ee)	*p*-MeC_6H_4	48	66 (*S*-(+)-**3b**)	92
3	Ph	*n*-Pr	A	(+)-**2b** (98% ee)	Ph	60	72 (*S*-(+)-**3c**)	91
4	Ph	*n*-Pr	A	(+)-**2b** (98% ee)	*p*-MeC_6H_4	60	75 (*S*-(+)-**3d**)	91
5	Ph	Me	B	(+)-**2c** (97% ee)	Ph	72	60 (*S*-(+)-**3a**)	93
6	Ph	Me	B	(+)-**2c** (97% ee)	*p*-MeC_6H_4	72	65 (*S*-(+)-**3b**)	95
7	Ph	Me	C	(−)-**2c** (98% ee)	Ph	60	66 (*R*-(−)-**3a**)	96
8	Ph	Me	C	(−)-**2c** (98% ee)	*p*-MeC_6H_4	60	72 (*R*-(−)-**3b**)	98
9	Ph	Me	C	(−)-**2c** (98% ee)	*p*-EC_6H_4[f]	60	58 (*R*-(−)-**3e**)	94
10[e]	*n*-Hep	H	A	(+)-**2e** (97% ee)	Ph	48	55 ((+)-**3f**)[g]	94

[a] The reaction was carried out using **2** (0.1 mmol), ArI (0.12 mmol), $Pd_2(dba)_3{\cdot}CHCCl_3$ (5 mol%), PPh_3 (20 mol%), and TBAB (0.1 mmol) in toluene (3 mL). [b] A = L-(−)-cinchonidine; B = L-(−)-α-methylbenzylamine; C = D-(+)-α-methylbenzylamine. [c] Ee value referring to the allene moiety determined by its conversion to ethyl ester by the treatment of **2** with EtI and *i*-Pr_2NEt in DMF at rt. [d] Ee values were determined by HPLC with Chiralcel OD column (0.46 cm ϕ × 25 cm). [e] MeCN was used as the solvent. [f] E = CO_2Me. [g] The absolute configuration not determined.

The absolute configurations of the allene moiety in *Sa*-(+)-**2f** and S-(+)-**3g** were determined by X-ray diffraction studies of the single crystals of the corresponding acid *Sa*-(+)-**1f** and S-(+)-**3g** using bromine atom as the reference.[10] The stereochemical outcome indicates that the mechanism may proceed via a mechanism shown in Scheme 2.

With these standard reaction conditions we studied the chirality transfer ability of this coupling-cyclization reaction in detail. The results are listed in Table 1. The following points are noteworthy: (1) the yields are moderate to good, with the highest being 90% (entry 1, Table 1); (2) the products **3** were formed in >90% ee, although somewhat lower than that of allene moiety in the 1 : 1 acid–base salts **2**; (3) the efficiency of chirality transfer process with L-(−)-α-methylbenzylamine is higher than that with L-(−)-cinchonidine (compare entries 1, 2 with 6, 7); (4) with D-(+)-α-methylbenzylamine, the efficiency of chirality transfer is even higher, and the products are the opposite enantiomers of what were formed with both L-(−)-α-methylbenzylamine and L-(−)-cinchonidine (entries 8–10, Table 1).

In conclusion, we have developed an efficient enantioselective synthesis of 3-aryl butenolides using the readily available chiral bases such as L-cinchonidine, D-(+)- and L-(−)-α-methylbenzylamine, as the chiral source. Through the X-ray diffraction study of the structures of *S*-(+)-**1f** and *S*-(+)-**3g**, it is concluded that the reaction may proceed *via* an oxidative–coordinative cyclization–reductive elimination process.

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10 The absolute configurations of (+)-**1f** and (+)-**3g** were determined by SHELXS software. CCDC 157278 and 157279. See http://www.rsc.org/suppdata/cc/b1/b109645a/ for crystallographic files in .cif or other format.