Asymmetric Catalysis Hot Paper

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Enantioselective Palladium-Catalyzed Insertion of α-Aryl-α-diazoacetates into the O–H Bonds of Phenols**

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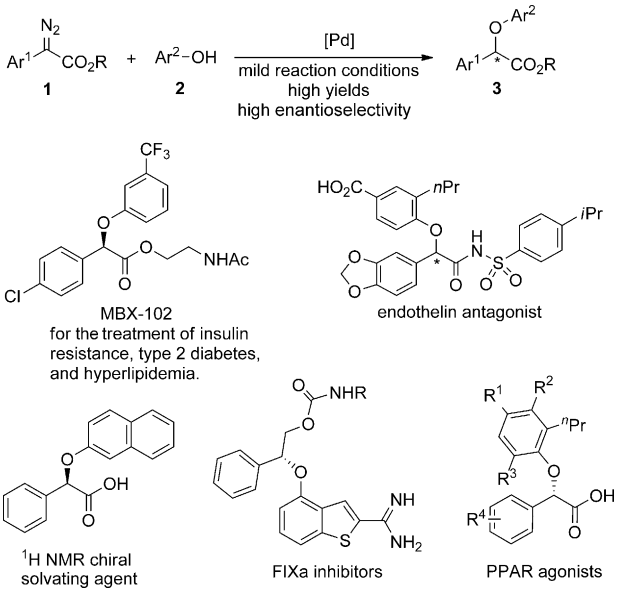
Abstract: *A palladium-catalyzed asymmetric O–H insertion reaction was developed. Palladium complexes with chiral spiro bisoxazoline ligands promoted the insertion of α-aryl-α-diazoacetates into the O–H bond of phenols with high yield and excellent enantioselectivity under mild reaction conditions. This palladium-catalyzed asymmetric O–H insertion reaction provided an efficient and highly enantioselective method for the preparation of synthetically useful optically active α-aryl-α-aryloxyacetates.*

Palladium is an indispensable and versatile catalyst in modern organic synthesis.[1] Palladium efficiently catalyzes the cyclopropanation of olefins with diazomethane, a widely used carbene-transfer reaction,[2] and various new palladium-catalyzed carbene-transfer reactions based on migratory insertion have recently been developed.[3] However, asymmetric palladium-catalyzed carbene-transfer reactions are rare and remain a challenge. The early examples of palladium-catalyzed asymmetric carbene-transfer reactions involved cyclopropanations and carbenylative amination, however, the resulting enantioselectivity was unsatisfactory.[4] Recently, Hu and co-workers[5] reported highly enantioselective palladium-catalyzed three-component reactions of pyrrole, diazoesters, and imines. Herein, we report a palladium-catalyzed asymmetric insertion of α-aryl-α-diazoacetates into the O–H bond of phenols (Scheme 1).[6] Palladium complexes with chiral spiro bisoxazoline ligands efficiently catalyzed the O–H insertion reaction, which provides a new method for the preparation of α-aryl-α-aryloxyacetates **3** with good yields and excellent enantioselectivity under mild, neutral reaction conditions.

The α-aryl-α-aryloxyacetate moiety is ubiquitous in biologically active molecules[7] and it is also present in a chiral solvating agent for NMR spectroscopy[8]



Scheme 1. Palladium-catalyzed asymmetric insertion of α-diazo-α--phenylacetates into the O–H bond of phenols, and selected important compounds derived from chiral α-aryl-α-aryloxyacetates.

(Scheme 1). The established methodologies for the synthesis of optically active α-aryl-α-aryloxyacetates are based on either multistep transformations from chiral starting materials or the use of chiral auxiliaries.[7,8] To our knowledge, no highly enantioselective catalytic asymmetric method for preparing these important compounds has been reported.[9] The challenges lie mainly in the high acidity of the α-hydrogen of α-aryl-α-aryloxyacetates. Because these compounds readily epimerize under basic conditions or at high temperature, any reliable method for their preparation should involve mild, neutral conditions. The transition-metal-catalyzed O–H insertion reaction meets this requirement. In 2006, Maier and Fu[6c] attempted an O–H bond insertion reaction between α-diazo-α-phenylacetates and phenols by using chiral copper bisazaferrocene complexes as catalysts. However, the desired O–H insertion product (α-phenoxy-α-phenylacetate) was obtained in 56% yield with only 11% *ee*. We[6d] and Uozumi and co-workers[6g] used chiral copper spiro bisoxazoline complexes and a chiral copper imidazoindolephosphine complex, respectively, for the same reaction and also obtained extremely low *ee* values (10% *ee* and 7% *ee*, respectively).

In this work, O–H bond insertion reactions between methyl α-diazo-α-phenylacetate (**1a**) and phenol (**2a**) were performed in chloroform at 40°C in the presence of various transition-metal catalysts prepared in situ from the corre-

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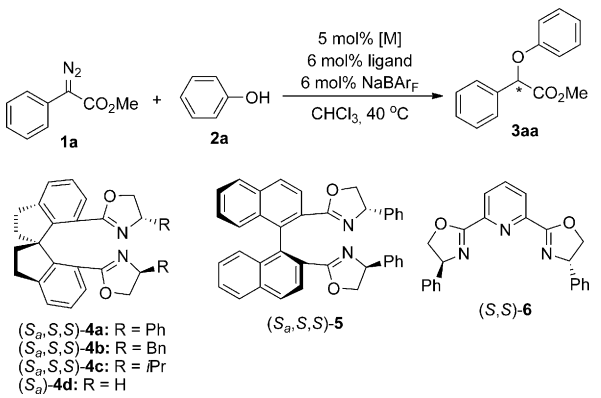
sponding metal salts and a chiral spiro bisoxazoline ligand (S_a,*S*,*S*)-**4a** with $NaBAr_F$[10] as an additive. As shown in Table 1, chiral catalysts derived from copper, iron, nickel, cobalt, gold, iridium, and ruthenium produced the desired O–H insertion product with low enantioselectivity (entries 1–7). By contrast, when $PdCl_2$ was used as the catalyst precursor, promising enantioselectivity (85% *ee*) was observed, although the yield was still low (entry 8). The nature of the palladium precursor strongly affected both the yield and the enantioselectivity of the reaction; $[Pd(CH_3CN)_2Cl_2]$ and $[Pd(PhCN)_2Cl_2]$, which have nitrile ligands, provided higher yields and enantioselectivities (entries 9 and 10).

Furthermore, $[Pd(CH_3CN)_2Cl_2]$ and $[Pd(PhCN)_2Cl_2]$ were stable under the reaction conditions, whereas palladium black formed when $PdCl_2$ was used. A Pd^0 precursor, $[Pd(dba)_2]$, gave a faster reaction but no chiral induction (entry 11).

Table 1: Palladium-catalyzed asymmetric O–H insertion of methyl α-diazo-α-phenylacetate into phenol.[a]



Entry	[M]	Ligand	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	CuCl	(S_a,*S*,*S*)-**4a**	3	71	10
2	$FeCl_2$	(S_a,*S*,*S*)-**4a**	24 (8)[e]	15	59
3	$NiCl_2$	(S_a,*S*,*S*)-**4a**	24 (8)[e]	11	22
4	$CoBr_2$	(S_a,*S*,*S*)-**4a**	24 (8)[e]	29	2
5	AuCl	(S_a,*S*,*S*)-**4a**	24 (8)[e]	12	22
6	$[Ir(COD)Cl]_2$	(S_a,*S*,*S*)-**4a**	24 (8)[e]	25	3
7	$[RuCl_2(benzene)]_2$	(S_a,*S*,*S*)-**4a**	15	10	36
8	$PdCl_2$	(S_a,*S*,*S*)-**4a**	18	23	85
9	$[Pd(CH_3CN)_2Cl_2]$	(S_a,*S*,*S*)-**4a**	18	51	87
10	$[Pd(PhCN)_2Cl_2]$	(S_a,*S*,*S*)-**4a**	11	47	92
11	$[Pd(dba)_2]$	(S_a,*S*,*S*)-**4a**	3.5	54	rac
12[f]	$[Pd(PhCN)_2Cl_2]$	(S_a,*S*,*S*)-**4a**	1.5	69	96
13[f,g]	$[Pd(PhCN)_2Cl_2]$	(S_a,*S*,*S*)-**4a**	2	83	98
14[g,h]	$[Pd(PhCN)_2Cl_2]$	(S_a,*S*,*S*)-**4a**	5	66	98
15[f,g]	$[Pd(PhCN)_2Cl_2]$	(S_a,*S*,*S*)-**4b**	1.5	66	97
16[f,g]	$[Pd(PhCN)_2Cl_2]$	(S_a,*S*,*S*)-**4c**	1.5	72	98
17[f,g]	$[Pd(PhCN)_2Cl_2]$	(S_a)-**4d**	5	72	95
18[f,g]	$[Pd(PhCN)_2Cl_2]$	(S_a,*S*,*S*)-**5**	2	74	90
19[f,g]	$[Pd(PhCN)_2Cl_2]$	(*S*,*S*)-**6**	2	74	19

[a] Reaction conditions: **1a**/**2a**/[M]/ligand/$NaBAr_F$ = 0.3:0.45:0.015:0.018:0.018 (mmol), in 4 mL solvent at 40 °C. [b] Yield of isolated product. [c] Determined by supercritical fluid chromatography (SFC) on a Chiralcel OD-H column. [d] The data is from Ref. [6d]. [e] The diazoester **1a** was not completely consumed after 24 h at 40 °C so the reaction was heated at 60 °C for additional 8 h. [f] With 12 mol% $NaBAr_F$. [g] With 300 mg 5 Å molecular sieves as additive. [h] With 1 mol% catalyst and 2.4 mol% $NaBAr_F$. COD = 1,5-cyclooctadiene, dba = dibenzylideneacetone.

Increasing the amount of $NaBAr_F$ to 2 equiv relative to $[Pd(PhCN)_2Cl_2]$ shortened the reaction time to 1.5 h and markedly improved both the yield and the enantioselectivity (entry 12). By contrast, the yield dropped dramatically to less than 10% in the absence of $NaBAr_F$. The role of $NaBAr_F$ remains unclear; however, the bulky and noncoordinating BAr_F anion of the resulting palladium catalyst may increase its Lewis acidity and stability, which is helpful for getting higher reactivity and enantioselectivity. Because an O–H insertion reaction with water was detected as a side reaction, molecular sieves were introduced to absorb the water in the reaction system and this change further increased the yield of desired product to 83% and the enantioselectivity to 98% *ee* (entry 13). The reaction could be performed at a catalyst loading of 1 mol% without compromising enantioselectivity; however, the reaction rate and yield decreased (entry 14). Ligands (S_a,*S*,*S*)-**4b**, (S_a,*S*,*S*)-**4c** and (S_a)-**4d** gave the same level of enantioselectivity (entries 15–17) as that of ligand (S_a,*S*,*S*)-**4a**, thus indicating that the substituents at the oxazoline rings have a negligible influence on the chiral induction of the catalyst. A bisoxazoline ligand with a binaphthyl backbone, (S_a,*S*,*S*)-**5**, also gave good yield and enantioselectivity (entry 18). However, a bisoxazoline ligand with a pyridine spacer, (*S*,*S*)-**6**, gave very low enantioselectivity (entry 19). The optical purity of product **3aa** remains unchanged even after stirring under the standard reaction conditions for an additional 20 h, a result that highlights the advantage of the current neutral and mild reaction conditions in the synthesis of α-aryl-α-aryloxyacetates.

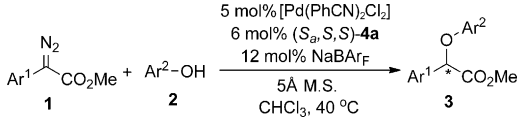
Under the optimal reaction conditions, various phenols and α-aryl-α-diazoacetates were evaluated as substrates (Table 2). Impressively, all the reactions exhibited good to high yields (68–89%) and excellent enantioselectivity (96–99% *ee*; entries 1–27). Although the highly sterically hindered reactants phenol **2k** and diazoester **1o** reduced the reaction rate (entries 11 and 27), the steric and electronic properties of the phenol and diazoester substituents had a negligible effect on the enantioselectivity, thus indicating that the spiro palladium catalyst is highly tolerant of various substrate structures. The broad substrate scope observed suggests that this reaction could prove a powerful method for the preparation of optically active α-aryl-α-aryloxyacetates. Moreover, a gram-scale synthesis of the insertion product **3aa** was performed with excellent yield and enantioselectivity (entry 28). This experiment further highlighted the potential of this palladium-catalyzed asymmetric O–H insertion reaction.

In addition to α-aryl-α-diazoacetates, ethyl and benzyl α-diazopropionates (**1p** and **1q**) also reacted with excellent enantioselectivity (96% *ee* and 94% *ee*, respectively), but the yields were low (Scheme 2).

In addition to phenols, other O–H donors, including *n*-butanol and water, were also tested (Scheme 3). The reactions of *n*-butanol and water proceeded smoothly to afford the corresponding O–H insertion products with moderate yields and enantioselectivity.

The O–H insertion products **3** could easily be transformed into various important chiral compounds (Scheme 4). For instance, the hydrolysis of methyl 2-(naphthalen-2-yloxy)-2-

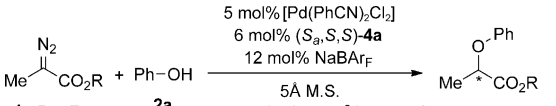
Table 2: Palladium-catalyzed asymmetric O–H insertion of α-aryl-α-diazoacetates into phenols.[a]



1 2 3

Entry	Ar^1 (**1**)	Ar^2 (**2**)	**3**	*t* [h]	Yield [%]	*ee* [%]
1	C_6H_5 (**1a**)	C_6H_5 (**2a**)	**3aa**	2	83	98(*R*)
2	C_6H_5 (**1a**)	4-$MeOC_6H_4$ (**2b**)	**3ab**	1.5	87	98
3	C_6H_5 (**1a**)	4-MeC_6H_4 (**2c**)	**3ac**	1.5	85	98
4	C_6H_5 (**1a**)	4-*t*BuC_6H_4 (**2d**)	**3ad**	1	86	98
5	C_6H_5 (**1a**)	4-PhC_6H_4 (**2e**)	**3ae**	0.7	83	99
6	C_6H_5 (**1a**)	4-ClC_6H_4 (**2f**)	**3af**	0.2	80	98
7	C_6H_5 (**1a**)	3-MeC_6H_4 (**2g**)	**3ag**	1.5	79	98
8	C_6H_5 (**1a**)	3-ClC_6H_4 (**2h**)	**3ah**	2	76	98
9	C_6H_5 (**1a**)	3-$CF_3C_6H_4$ (**2i**)	**3ai**	0.2	74	97
10	C_6H_5 (**1a**)	2-MeC_6H_4 (**2j**)	**3aj**	0.2	78	98
11	C_6H_5 (**1a**)	2,6-$Me_2C_6H_4$ (**2k**)	**3ak**	12	69	97
12	C_6H_5 (**1a**)	2-naphthyl (**2l**)	**3al**	0.2	84	99(*R*)
13	4-MeC_6H_4 (**1b**)	C_6H_5 (**2a**)	**3ba**	0.2	78	98
14	4-PhC_6H_4 (**1c**)	C_6H_5 (**2a**)	**3ca**	0.5	82	98
15	4-ClC_6H_4 (**1d**)	C_6H_5 (**2a**)	**3da**	2	87	98
16	4-BrC_6H_4 (**1e**)	C_6H_5 (**2a**)	**3ea**	1	79	98
17	3-$MeOC_6H_4$ (**1f**)	C_6H_5 (**2a**)	**3fa**	2	86	99
18	3-MeC_6H_4 (**1g**)	C_6H_5 (**2a**)	**3ga**	1	77	97
19	3-ClC_6H_4 (**1h**)	C_6H_5 (**2a**)	**3ha**	3.5	81	97
20	3-$CF_3C_6H_4$ (**1i**)	C_6H_5 (**2a**)	**3ia**	5	77	98
21	2-MeC_6H_4 (**1j**)	C_6H_5 (**2a**)	**3ja**	2.5	77	98
22	2-ClC_6H_4 (**1k**)	C_6H_5 (**2a**)	**3ka**	1	81	96
23	2-naphthyl (**1l**)	C_6H_5 (**2a**)	**3la**	2	68	97
24	3-thienyl (**1m**)	C_6H_5 (**2a**)	**3ma**	0.5	79	99
25	4-ClC_6H_4 (**1d**)	3-$CF_3C_6H_4$ (**2i**)	**3di**	2	85	96(*R*)
26[b]	**1n**	C_6H_5 (**2a**)	**3na**	4	89	96
27[c]	**1o**	C_6H_5 (**2a**)	**3oa**	8	87	98
28[d]	C_6H_5 (**1a**)	C_6H_5 (**2a**)	**3aa**	4	92	99(*R*)

[a] The reaction conditions and analysis were the same as for Table 1, entry 13. The diazoesters **1** were slowly added over 2 h by using a syringe pump. For entries 1–3 and 7, the diazoesters was added in one portion. See the Supporting Information for details. The absolute configurations of products **3aa**, **3al**, and **3na** were determined according to reported procedures.[11] [b] **1n** = benzyl 2-diazo-2-phenylacetate. [c] **1o** = *tert*-butyl 2-diazo-2-phenylacetate. [d] Performed on a gram-scale: **1a**/**2a**/[Pd-$(PhCN)_2Cl_2$]/(S_a,*S*,*S*)-**4a**/$NaBAr_F$ = 6:9:0.3:0.36:0.36 (mmol); 21 mL $CHCl_3$; 1.0 g 5 Å molecular sieves; **1a** was dissolved in 5 mL $CHCl_3$ and slowly added over 2 h by using a syringe pump. 1.34 g **3aa** was obtained.



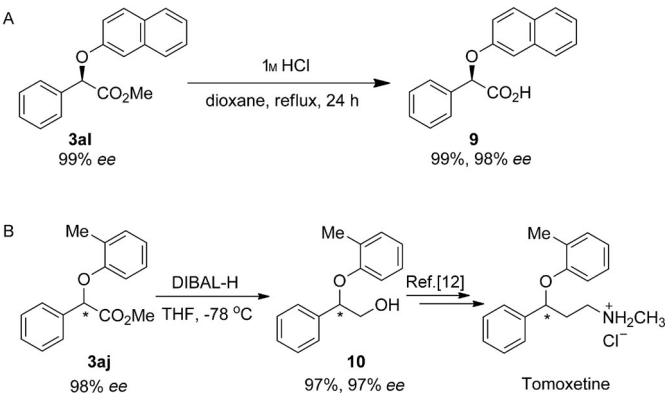
1p R = Et, **1q** R = Bn — **2a** — **3pa** 21%, 96% *ee*; **3qa** 34%, 94% *ee*

Scheme 2. Palladium-catalyzed asymmetric O–H insertion of ethyl and benzyl α-diazopropionates into phenol.

phenylacetate (**3al**) in acidic media produced acid **9**, an important chiral solvating reagent for NMR spectroscopy, in quantitative yield with retained optical purity. The reduction of methyl α-phenyl-α-(*o*-tolyloxy)acetate (**3aj**) gave alcohol **10** (97% yield), which was easily transformed into tomoxetine, a well-known chiral drug for the treatment of psychiatric disorders.[12]

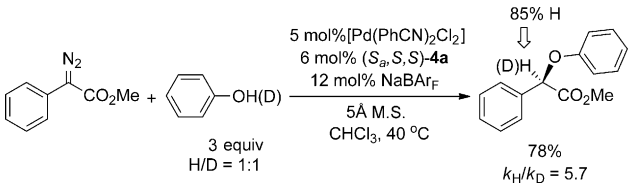
1a — **7**, R = *n*Bu 2 h, 74%, 72% *ee*; **8**, R = H 1 h, 64%, 36% *ee*

Scheme 3. Palladium-catalyzed asymmetric O–H insertion into *n*-butanol and water.



Scheme 4. Transformations of the insertion products. DIBAL-H = diisobutylaluminum hydride, THF = tetrahydrofuran.

The detailed mechanism of the palladium-catalyzed asymmetric O–H insertion reaction is unclear. A preliminary study showed that the reaction exhibits a significant first-order kinetic isotope effect (Scheme 5), thus indicating that the breaking of the phenolic O–H bond or the formation of the C–H bond in the product was involved in the rate-determining step.



Scheme 5. Kinetic isotope effect.

In summary, a palladium-catalyzed asymmetric O–H bond insertion reaction between α-aryl-α-diazoacetates and phenols was developed. Palladium complexes of chiral spiro bisoxazoline ligands were shown to be efficient and highly enantioselective catalysts for the reaction. The reaction provides a mild, neutral method for the preparation of chiral α-aryl-α-aryloxyacetates and broadens the application of palladium catalysts in carbene transformations.

Experimental Section

Typical procedure for palladium-catalyzed O–H insertion: powdered $PdCl_2(PhCN)_2$ (5.8 mg, 0.015 mmol, 5 mol%), (S_a,*S*,*S*)-**4a** (9.2 mg, 0.018 mmol, 6 mol%), $NaBAr_F$ (33.8 mg, 0.036 mmol, 12 mol%) and 0.3 g 5 Å molecular sieves were introduced into an oven-dried Schlenk tube in an argon-filled glovebox. After $CHCl_3$ (3 mL) was

injected into the Schlenk tube, the solution was stirred at room temperature under an argon atmosphere for 2 h. *o*-Cresol (49 mg, 0.45 mmol) was added to the reaction mixture at 40 °C. Then a solution of methyl 2-diazo-2-phenylacetate (52.8 mg, 0.3 mmol) in 1 mL $CHCl_3$ was introduced into the reaction mixture by a syringe pump over 2 h. The resulting mixture was continually stirred at 40 °C until the full consumption of **1a** was fully consumed. After filtering and removing the solvent under vacuum, the product was isolated by flash chromatography (petroleum ether/ethyl acetate = 10:1, v/v) as a colorless oil and the *ee* value was determined by SFC with a chiral column.

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Keywords: α-aryl-α-aryloxyacetates · asymmetric catalysis · bisoxazoline ligands · carbenes · palladium

[1] J. Tsuji, *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, Wiley, Chichester, **2005**.

[2] For reviews, see: a) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**, chap. 4; b) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977.

[3] For selected examples, see: a) K. L. Greenman, D. S. Carter, D. L. Van Vranken, *Tetrahedron* **2001**, *57*, 5219; b) S. K. J. Devine, D. L. Van Vranken, *Org. Lett.* **2007**, *9*, 2047; c) J. Barluenga, P. Moriel, C. Valdés, F. Aznar, *Angew. Chem.* **2007**, *119*, 5683; *Angew. Chem. Int. Ed.* **2007**, *46*, 5587; d) C. Peng, Y. Wang, J.-B. Wang, *J. Am. Chem. Soc.* **2008**, *130*, 1566; e) Z.-H. Zhang, Y.-Y. Liu, M.-X. Gong, X.-K. Zhao, Y. Zhang, J.-B. Wang, *Angew. Chem.* **2010**, *122*, 1157; *Angew. Chem. Int. Ed.* **2010**, *49*, 1139; f) L. Zhou, F. Ye, Y. Zhang, J.-B. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 13590; g) Z.-S. Chen, X.-H. Duan, P.-X. Zhou, S. Ali, J.-Y. Luo, Y.-M. Liang, *Angew. Chem.* **2012**, *124*, 1399; *Angew. Chem. Int. Ed.* **2012**, *51*, 1370; For a review, see: h) Y. Zhang, J.-B. Wang, *Eur. J. Org. Chem.* **2011**, 1015.

[4] a) S. E. Denmark, R. A. Stavenger, A.-M. Faucher, J. P. Edwards, *J. Org. Chem.* **1997**, *62*, 3375; b) D.-J. Cho, S.-J. Jeon, H.-S. Kim, C.-S. Cho, S.-C. Shim, T.-J. Kim, *Tetrahedron: Asymmetry* **1999**, *10*, 3833; c) A. Khanna, C. Maung, K. R. Johnson, T. T. Luong, D. L. Van Vranken, *Org. Lett.* **2012**, *14*, 3233.

[5] D. Zhang, H. Qiu, L.-Q. Jiang, F.-P. Lv, C.-Q. Ma, W.-H. Hu, *Angew. Chem.* **2013**, *125*, 13598; *Angew. Chem. Int. Ed.* **2013**, *52*, 13356.

[6] For a non-asymmetric palladium-catalyzed O-H insertion reaction, see: a) M. Kitamura, M. Kisanuki, R. Sakata, T. Okauchi, *Chem. Lett.* **2011**, *40*, 1129; For a diastereoselective palladium-catalyzed N-H insertion reaction, see: b) G. Liu, J. Li, L. Qiu, L. Liu, G.-Y. Xu, B. Ma, J.-T. Sun, *Org. Biomol. Chem.* **2013**, *11*, 5998; For enantioselective O-H insertion reactions catalyzed by other catalysts, see: c) T. C. Maier, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 4594; d) C. Chen, S.-F. Zhu, B. Liu, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2007**, *129*, 12616; e) S.-F. Zhu, Y. Cai, H.-X. Mao, J.-H. Xie, Q.-L. Zhou, *Nat. Chem.* **2010**, *2*, 546; f) H. Saito, R. Iwai, T. Uchiyama, M. Miyake, S. Miyairi, *Chem. Pharm. Bull.* **2010**, *58*, 872; g) T. Osako, D. Panichakul, Y. Uozumi, *Org. Lett.* **2012**, *14*, 194; h) S.-F. Zhu, Q.-L. Zhou, *Acc. Chem. Res.* **2012**, *45*, 1365; i) X.-G. Song, S.-F. Zhu, X.-L. Xie, Q.-L. Zhou, *Angew. Chem.* **2013**, *125*, 2615; *Angew. Chem. Int. Ed.* **2013**, *52*, 2555.

[7] a) D. L. Williams, K. L. Murphy, N. A. Nolan, J. A. O'Brien, D. J. Pettibone, S. D. Kivlighn, S. M. Krause, E. V. Lis, G. J. Zingaro, R. A. Gabel, *J. Pharmacol. Exp. Ther.* **1995**, *275*, 1518; b) R. Kucznierz, F. Grams, H. Leinert, K. Marzenell, R. A. Engh, W. von der Saal, *J. Med. Chem.* **1998**, *41*, 4983; c) K. L. Luskey, J. Luo, US6262118, **2001**; d) A. D. Adams, Z. Hu, D. von Langen, A. Dadiz, A. Elbrecht, K. L. MacNaul, J. P. Berger, G. Zhou, T. W. Doebber, R. Meurer, M. J. Forrest, D. E. Moller, A. B. Jones, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3185; e) G. Q. Shi, J. F. Dropinski, B. M. McKeever, S. Xu, J. W. Becker, J. P. Berger, K. L. MacNaul, A. Elbrecht, G. Zhou, T. W. Doebber, P. Wang, Y.-S. Chao, M. Forrest, J. V. Heck, D. E. Moller, A. B. Jones, *J. Med. Chem.* **2005**, *48*, 4457; f) E. N. Koini, P. Papazafiri, A. Vassilopoulos, M. Koufaki, Z. Horváth, I. Koncz, L. Virág, G. J. Papp, A. Varró, T. Calogeropoulou, *J. Med. Chem.* **2009**, *52*, 2328; g) S. Wang, R. Beck, A. Burd, T. Blench, F. Marlin, T. Ayele, S. Buxton, C. Dagostin, M. Malic, R. Joshi, J. Barry, M. Sajad, C. Cheung, S. Shaikh, S. Chahwala, C. Chander, C. Baumgartner, H.-P. Holthoff, E. Murray, M. Blackney, A. Giddings, *J. Med. Chem.* **2010**, *53*, 1473.

[8] a) G. Carbonara, A. Carocci, G. Fracchiolla, C. Franchini, G. Lentini, F. Loiodice, P. Tortorella, *ARKIVOC* **2004**, *v*, 5; b) M. M. Cavalluzzi, C. Bruno, G. Lentini, A. Lovece, A. Catalano, A. Carocci, C. Franchini, *Tetrahedron: Asymmetry* **2009**, *20*, 1984.

[9] For diastereoselective synthesis of chiral α-aryl-α-aryloxyacetates, see: a) K. Koh, T. Durst, *J. Org. Chem.* **1994**, *59*, 4683; b) P. N. Devine, U.-H. Dolling, R. M. Heid, Jr., D. M. Tschaen, *Tetrahedron Lett.* **1996**, *37*, 2683; For enzyme-catalyzed kinetic resolution, see: c) A. Ammazzalorso, R. Amoroso, G. Bettoni, B. De Filippis, M. Fantacuzzi, L. Giampietro, C. Maccallini, M. L. Tricca, *Chirality* **2008**, *20*, 115.

[10] Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

[11] a) T. Shintou, T. Mukaiyama, *J. Am. Chem. Soc.* **2004**, *126*, 7359; b) M. E. Sanders, D. B. Karpf, WO 2006102375A2, **2006**; c) G. Massolini, G. Fracchiolla, E. Calleri, G. Carbonara, C. Temporini, A. Lavecchia, S. Cosconati, E. Novellino, F. Loiodice, *Chirality* **2006**, *18*, 633.

[12] P. N. Devine, R. M. Heid, Jr., D. M. Tschaen, *Tetrahedron* **1997**, *53*, 6739.

