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Catalytic Enantioselective Synthesis of Chiral Phthalides by Efficient Reductive Cyclization of 2-Acylarylcarboxylates under Aqueous Transfer Hydrogenation Conditions

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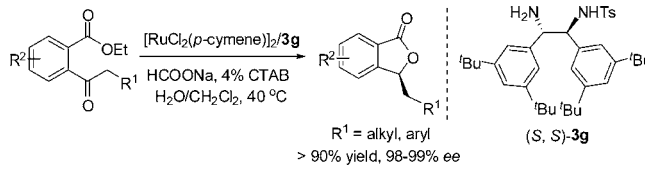
ABSTRACT



A new diamine ligand for asymmetric transfer hydrogenation (ATH) was discovered. The reductive cyclization of 2-acylarylcarboxylates was found to proceed highly stereoselectively by the new Ru complex-catalyzed ATH and subsequent in situ lactonization under aqueous conditions. It enables efficient access to a wide variety of 3-substituted phthalides in enantiomerically pure form.

Phthalide (1(3*H*)-isobenzofuranone) frameworks are present in a large number of natural products and biologically active compounds.[1] Chiral 3-substituted phthalides therefore are very useful molecules as valuable pharmacological compounds and versatile building blocks for medicinal chemistry.[2] Over the past two decades, there have been considerable efforts in the asymmetric synthesis of chiral phthalides, and a variety of methods toward introducing C-3 chirality have been developed.[3,4] Among them, catalytic approaches appear to be the most atom economic and thus are of particular interest. Accordingly, catalytic asymmetric reduction in combination with the in situ lactonization of 2-acylarylcarboxylate compounds represents an attractive and efficient strategy for chiral phthalide synthesis. However, to our knowledge, only a few reports on the synthesis of chiral

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(1) (a) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds;* Academic Press: New York, 1975; Vol. 1, pp 249−264. (b) Beck, J. J.; Chou, S.-C. *J. Nat. Prod.* **2007**, *70*, 891. (c) Atta-ur-Rahman, H. E. J. *Studies in Natural Products Chemistry: Bioactive Natural Products (Part L)*; Elsevier Science, 2006; Vol 32.

(2) (a) Knepper, K.; Ziegert, R. E.; Bräse, S. T. *Tetrahedron* **2004**, *60*, 8591. (b) Witulski, B.; Zimmermann, A.; Gowans, N. D. *Chem. Commun.* **2002**, 2984. (c) Hung, T. V.; Mooney, B. A.; Prager, R. H.; Tippett, J. M. *Aust. J. Chem.* **1981**, *34*, 383.

(3) For selected examples, see: (a) Karnik, A. V.; Kamath, S. S. *Synthesis* **2008**, 1832. (b) Tanaka, K.; Osaka, T.; Noguchi, K.; Hirano, M. *Org. Lett.* **2007**, *9*, 1307. (c) Pedrosa, R.; Sayaleroy, S.; Vicente, M. *Tetrahedron* **2006**, *62*, 10400. (d) Kosaka, M.; Sekiguchi, S.; Naito, J.; Uemura, M.; Kuwahara, S.; Watanabe, M.; Harada, N.; Hiroi, K. *Chirality* **2005**, *17*, 218. (e) Witulski, B.; Zimmermann, A. *Synlett* **2002**, 1855. (f) Takahashi, M.; Sekine, N.; Fujita, T.; Watanabe, S.; Yamaguchi, K.; Sakamoto, M. *J. Am. Chem. Soc.* **1998**, *120*, 12770. (g) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Giaroni, P. *J. Org. Chem.* **1992**, *57*, 782. (h) Watanabe, M.; Hashimoto, N.; Araki, S.; Butsugan, Y. *J. Org. Chem.* **1992**, *57*, 742. (i) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Synthesis* **1992**, 681. (j) Ogawa, Y.; Hosaka, K.; Chin, M.; Mitsuhashi, H. *Heterocycles* **1989**, *29*, 865. (k) Kitayama, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3765. (l) Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 2205. (m) Meyers, A. I.; Hanagan, M. A.; Trefonas, L. M.; Baker, R. J. *Tetrahedron* **1983**, *39*, 1991.

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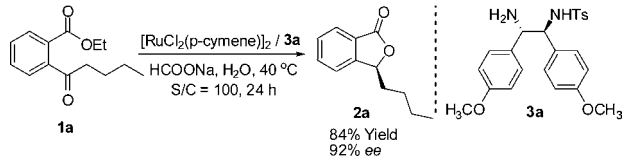
phthalides by catalytic hydrogenation and transfer hydrogenation have been realized to date.[4] There still remains a significant need for a more practical process with broader substrate scope and higher reaction stereoselectivity. In this communication, we report a highly enantioselective synthesis of 3-substituted phthalides by efficient reductive cyclization of 2-acylarylcarboxylates under ruthenium-catalyzed aqueous asymmetric transfer hydrogenation conditions using a novel chiral vicinal diamine ligand.

Since the breakthrough by Noyori and co-workers,[5] transition-metal-catalyzed asymmetric transfer hydrogenation has been shown to be one of the most powerful and common methods for the reduction of carbonyl compounds.[6] However, despite the extensive studies of asymmetric reduction of acetophenone derivatives using various catalysts, transfer hydrogenation of 2′-substituted acetophenones has been less developed. In most documented examples,[5a,7,10a] reduced enantioselectivities were often observed with these substrates probably due to the disturbance of the key transition state by the *ortho*-substituent. In 2001, the asymmetric transfer hydrogenation of methyl 2-acylbenzoates in ^{i}PrOH using ruthenium catalysts has been carefully studied,[4c] but the results remained unsatisfactory. Inspired by the previous success of vicinal diamine preparation,[8] we became intrigued by the possibility of tuning catalyst functionality by introducing a new diamine backbone for enantioselective synthesis of 3-substituted phthalides via asymmetric transfer hydrogenation.

Scheme 1. Synthesis of 3-Butylphthalide **2a** by Ru−**3a** Catalyzed Transfer Hydrogenation



We chose to examine ethyl 2-pentanoylbenzoate (**1a**) as the initial substrate, as the resulting product 3-butylphthalide (**2a**) is a useful medical agent for the treatment of brain-related neuro diseases such as ischemic stroke.[9] First, we sought an effective reaction system. The preliminary investigation revealed that the asymmetric transfer hydrogenation of **1a** can proceed successfully in water with sodium formate as hydride donor[10] by the in situ formed Ru−**3a** catalyst (84% yield, 92% ee) (Scheme 1); both of the other two general conditions in ^{i}PrOH and HCOOH−NEt_3 were found not ideal due to competitive side reactions or poor conversion. When Noyori's catalyst *N*-(*p*-toluenesulfonyl)-1,2-diphenyl-ethylenediamine)/Ru(II) complex (Ru−TsDPEN) was used to catalyze the same reaction in water, a similar enantioselectivity was observed (92.7%) after 24 h, but the yield was much lower (68%). These results prompted us to envision potential utilization of other 1,2-diaryl-ethylenediamine/Ru(II) complexes as excellent catalysts for this practical aqueous asymmetric transfer hydrogenation. Accordingly, a new family of chiral diamine ligands (**3b**−**g**) that incorporate both electronic and steric factors were prepared using the established method[8] (Figure 1).

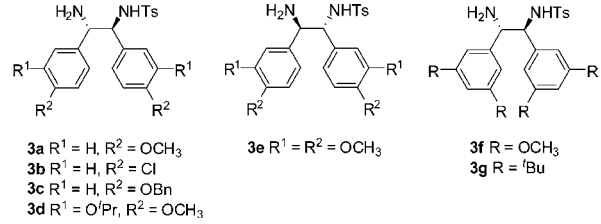


Figure 1. Chiral diamine ligands **3a**−**g**.

Screening of the obtained chiral diamine ligands in the above reductive cyclization of ethyl 2-pentanoylbenzoate (**1a**) was next carried out in aqueous HCOONa at 40 °C, and the results are summarized in Table 1. Simple modification of the substituents at the 4,4′-positions on the aryl ring with both electronic and steric changes did not afford the product with higher enantioselectivity (entries 3 and 4 vs 2). Gratifyingly, when more sterically hindered diamine ligands

(4) Catalytic hydrogenation: (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509. Transfer hydrogenation: (c) Everaere, K.; Scheffler, J.-L.; Mortreux, A.; Carpentier, J.-F. *Tetrahedron Lett.* **2001**, *42*, 1899. For examples of Ni-catalyzed cross-couplings, see: (d) Lei, J.-G.; Hong, R.; Yuan, S.-G.; Lin, G.-Q. *Synlett* **2002**, 927. (e) Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. *Chem.—Eur. J.* **2007**, *13*, 4356.

(5) (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (c) Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1996**, 233. (d) Haack, K. J.; Hashikuchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285.

(6) For reviews, see: (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (c) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67. (d) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201. (e) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (f) Wu, X. F.; Xiao, J. L. *Chem. Commun.* **2007**, 2449. (g) Wang, C.; Wu, X. F.; Xiao, J. L. *Chem. Asian J.* **2008**, *3*, 1750.

(7) (a) Alonso, D. A.; Nordin, S. J. M.; Roth, P.; Tarnai, T.; Andersson, P. G. *J. Org. Chem.* **2000**, *65*, 3116. (b) Matharu, D. S.; Morris, D. J.; Kawamoto, A. M.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2005**, *7*, 5489. (c) Wang, F.; Liu, H.; Cun, L.-F.; Zhu, J.; Deng, J.-G.; Jiang, Y.-Z. *J. Org. Chem.* **2005**, *70*, 9424. (d) Mao, J.-C.; Wan, B.-S.; Wu, F.; Lu, S.-W. *Tetrahedron Lett.* **2005**, *46*, 7341. (e) Morris, D. J.; Hayes, A. M.; Wills, M. *J. Org. Chem.* **2006**, *71*, 7035. (f) Li, X. H.; Blacker, J.; Houson, I.; Wu, X. F.; Xiao, J. L. *Synlett* **2006**, 1155.

(8) (a) Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 3953. (b) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831.

(9) (a) Barton, D. H. R.; de Vries, J. X. *J. Chem. Soc.* **1963**, 1916. (b) Zhu, X. Z.; Li, X. Y.; Liu, J. *Eur. J. Pharmacol.* **2004**, *500*, 221. (c) Chang, Q.; Wang, X. L. *Acta Pharmacol. Sin.* **2003**, *24*, 796. (d) Wang, X. W. *Drugs Future* **2000**, *25*, 16. (e) Huang, X. X.; Hu, D.; Qu, Z. W.; Zhang, J. T.; Feng, Y. P. *Yaoxue Xuebao* **1996**, *31*, 246.

(10) For leading references of asymmetric transfer hydrogenation by HCOONa in water, see: (a) Wu, X.; Li, X.; Hems, W.; King, F.; Xiao, J. L. *Org. Biomol. Chem.* **2004**, *2*, 1818. (b) Wu, X.; Li, X.; King, F.; Xiao, J.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3407. (c) Wu, X. F.; Vinci, D.; Ikariya, T.; Xiao, J. L. *Chem. Commun.* **2005**, 4447. (d) Wu, X. F.; Li, X. H.; Zanotti-Gerosa, A.; Pettman, A.; Liu, J.; Mills, A. J.; Xiao, J. L. *Chem.—Eur. J.* **2008**, *14*, 2209. For an excellent review, see ref 6f.

3d−**g** were used, much increased enantioselectivities were observed (entries 5−8). It appeared that the steric property of the substituents on the diphenyl backbone had an obvious impact on the reaction enantioselectivity. Among those diamines examined, **3g** (TsDBuPEN) having four bulky *tert*-butyl groups at the 3,3′- and 5,5′-positions of the phenyl moieties proved to be the best ligand, giving the corresponding (*S*)-3-butylphthalide ((*S*)-**2a**) with 98% ee (entry 8). Further studies with an added surfactant showed that the use of 4 mol % of CTAB (cetyltrimethylammonium bromide) was greatly helpful in accelerating the reaction and achieving an excellent yield while maintaining the enantioselectivity (92% yield, 98% ee, entry 9). Other surfactants such as Tween 20, Triton X100, SDS, and TBAB were all not superior to CTAB.[11] Notably, in an experiment with lower catalyst loading (0.5 mol %, S/C = 200) of **3g** (TsDBuPEN) under the optimal conditions, the same excellent yield (92%) and enantioselectivity (98%) could be achieved as well after prolonged (16 h) reaction (entry 10).

Table 1. Catalytic Effects of the Chiral Diamine Ligands **3a**−**g**[a]

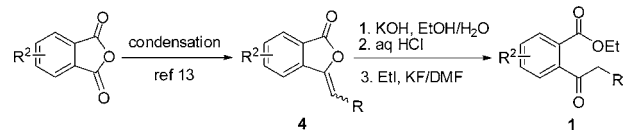
entry	ligand	time (h)	additive	yield (%)[b]	ee (%)[c,d]
1	(*R*,*R*)-TsDPEN	24	-	68	93 (*R*)
2	(*S*,*S*)-**3a**	24	-	84	92 (*S*)
3	(*S*,*S*)-**3b**	24	-	63[e]	86 (*S*)
4	(*S*,*S*)-**3c**	24	-	83	90 (*S*)
5	(*S*,*S*)-**3d**	24	-	95	95 (*S*)
6	(*R*,*R*)-**3e**	24	-	76	95 (*R*)
7	(*S*,*S*)-**3f**	24	-	83	95 (*S*)
8	(*S*,*S*)-**3g**	24	-	61[e]	98 (*S*)
9	(*S*,*S*)-**3g**	8.5	CTAB[g]	92	98 (*S*)
10[f]	(*S*,*S*)-**3g**	16	CTAB[g]	92	98 (*S*)

[a] Unless otherwise noted, all the reactions were performed with 0.5 mmol of **1a**, 5 equiv of HCOONa, and in situ prepared Ru−**3** (1 mol %, S/C = 100), in 1 mL of H_2O at 40 °C. [b] Isolated yield. [c] Determined by HPLC on a chiral column. [d] The configuration was determined by comparing the $[\alpha]_D$ with known data. [e] Not full conversion of **1a** after 24 h. [f] 1.0 mmol of **1a**, with 0.5 mol % of Ru−**3g** (S/C = 200). [g] 4 mol % was used.

To explore this transfer hydrogenation in a broad range of substrates, we improved the synthesis of 2-acylarylcarboxylates. The general procedure[12] for the preparation of 2-acylbenzoic acids by the reaction of phthalic anhydride with cadmium reagents has to face the low yield, poor operability, and high toxicity. Taking advantage of the condensation methods for alkenylphthalides (**4**) synthesis from related phthalic anhydrides,[13a] a variety of ethyl 2-acylarylcarboxylates (**1**) were easily accessed by a one-pot, three-step sequence reaction (Scheme 2).

With the optimized conditions identified and diverse substrates in hand, the scope and generality of the reaction were then investigated (Table 2). In all examples, the transfer

Scheme 2. Improved Synthesis of 2-Acylarylcarboxylates **1**



hydrogenation followed by in situ lactonization went smoothly, giving the desired phthalide products in over 90% isolated yields with uniformly high enantioselectivities (98−99%). It appeared that both the ee and yield were not sensitive to the R^1 and R^2 substitution. The reactions of the 2-acylarylcarbonylates **1e**−**u**, which bear aromatic R^1 substituents at the acyl moiety, were carried out in aqueous HCOONa with CH_2Cl_2 as cosolvent to accelerate the conversion further (entries 4−21). This is due to the relatively poor aqueous solubilities of these substrates as they are mostly in solid or viscous liquid state. It is noteworthy that, in the case of **1e**, very high enantioselectivity (99%) was again maintained under much reduced catalyst loading of 0.2 mol % (entry 5). Several heteroatom-containing enantiomerically enriched phthalides **2m**, **2o**, **2p**, and **2q** were also obtained (entries 13 and 15−17), which might be interesting for biological screening. Assuming an analogous reaction mechanism, the absolute stereochemistry of the newly formed carbon center was assigned as in the structure by comparison of optical rotation value with that reported for **2a**, **2b**, **2c**, and **2e**.[14,3c,l]

We believe that the origins of the excellent stereocontrol come from the more preferable chirality-determining transition state of the Ru−TsDBuPEN (**3g**) complex with the ethyl 2-acylarylcarboxylate substrates, although the exact model remains unclear.[15] In addition, as illustrated in Figure 2, a possible hydrogen bonding involvement of the neighboring ester function group of the 2-acylarylcarboxylate substrate might also be responsible for the observed selectivity. It was found that the ee (59%) dramatically dropped with 2-methylacetophenone as substrate, which has an *ortho*-methyl group instead of a carbonyl-containing ester group. Moreover, phthalide was the only product observed during the reaction, suggesting a very good cooperative processing of the asymmetric reduction and lactonization.

(11) Abbreviations: Tween 20 is polyoxyethylene sorbitan monolaurate; Triton X100 is polyethylene glycol *p*-(1,1,3,3-tetramethylbutyl)-phenyl ether; SDS is sodium monododecyl sulfate; TBAB is tetrabutylammonium bromide.

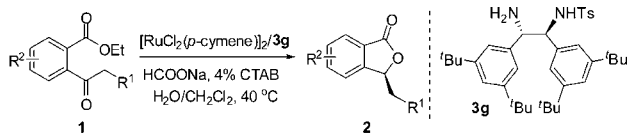
(12) (a) de Benneville, P. L. *J. Org. Chem.* **1941**, *6*, 462. (b) Mitra, R. B.; Kulkarni, G. H.; Khanna, P. N. *Synthesis* **1977**, 415.

(13) Representative methods: (a) Shriner, R. L.; Keyser, L. S *J. Org. Chem.* **1940**, *5*, 200. (b) Castro, C. E.; Gaughan, E. G.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071. (c) Weiss, R. *Org. Synth.* **1943**, *2*, 61. Improved methods: (d) Patil, S. R. *Synth. Commun.* **1990**, *20*, 167. (e) Lácová, M.; Chovancová, J.; Veverková, E.; Toma, Š *Tetrahedron* **1996**, *52*, 14995. (f) Safari, J.; Naeimi, H.; Khakpour, A. A.; Jondani, R. S.; Khalili, S. D. *J. Mol. Catal. A* **2007**, *270*, 236. (g) Landge, S. M.; Berryman, M.; Török, B. *Tetrahedron Lett.* **2008**, *49*, 4505.

(14) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Chem. Pharm. Bull.* **1991**, *39*, 3136.

(15) For related mechanistic studies on asymmetric transfer hydrogenation, see: (a) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466. (b) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931. (c) Sandoval, C. A.; Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Noyori, R. *Chem. Asian. J.* **2006**, *1*−*2*, 102. (d) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580. (e) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237. (f) Handgraaf, J.-W.; Meijer, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 3099. (g) Wu, X. F.; Liu, J. K.; Tommaso, D. D.; Iggo, J. A.; Catlow, C. R. A.; Bacsa, J.; Xiao, J. L. *Chem.*−*Eur. J.* **2008**, *14*, 7699.

Table 2. Asymmetric Synthesis of 3-Substituted Phthalides by Ru−TsDBuPEN (**3g**) Catalyzed Transfer Hydrogenation[a]



entry	substrate **1**	t (h)	**2**	yield (%)[d]	ee (%)[e]
1[b]	**1b**: R^1 = H, R^2 = H	10	**2b**	97	98
2[b]	**1c**: R^1 = CH_3, R^2 = H	15	**2c**	95	98
3[b]	**1d**: R^1 = $ClCH_2(CH_2)_2$, R^2 =H	18	**2d**	95	99
4	**1e**: R^1 = Ph, R^2 = H	4	**2e**	96	99
5[c]	**1e**: R^1 = Ph, R^2 = H	24	**2e**	92	99
6	**1f**: R^1 = 4-ClC_6H_4, R^2 = H	4	**2f**	98	99
7	**1g**: R^1 = 4-MeC_6H_4, R^2 = H	4	**2g**	93	99
8	**1h**: R^1 = 4-$MeOC_6H_4$, R^2 = H	4	**2h**	96	99
9	**1i**: R^1 = 4-$MeSC_6H_4$, R^2 = H	4	**2i**	99	99
10	**1j**: R^1 = 4-$CF_3C_6H_4$, R^2 = H	4	**2j**	96	99
11	**1k**: R^1 = 3,5-$F_2C_6H_3$, R^2 = H	4	**2k**	98	99
12	**1l**: R^1 = 3,4-$(MeO)_2C_6H_3$, R^2 = H	4	**2l**	93	99
13	**1m**: R^1 = 2-thienyl, R^2 = H	4	**2m**	97	99
14	**1n**: R^1 = 1-naphthyl, R^2 = H	11	**2n**	98	99
15	**1o**: R^1 = 4-quinolyl, R^2 = H	12	**2o**	94	98
16	**1p**: R^1 = 4-Cl-phenoxyl, R^2 = H	4	**2p**	94	98
17	**1q**: R^1 = 4-Cl-phenylthio, R^2 = H	4	**2q**	97	98
18	**1r**: R^1 = Ph, R^2 = 4-Br	5	**2r**	90	99
19	**1s**: R^1 = Ph, R^2 = 5-Br	4	**2s**	93	99
20	**1t**: R^1 = Ph, R^2 = 4,5-Cl_2	4	**2t**	98	98
21	**1u**: R^1 = Ph, R^2 = 4,5-C_4H_4	4	**2u**	97	98

[a] The reactions were performed with 0.5 mmol of **1**, 5 equiv of HCOONa, 4 mol % of CTAB, and in situ prepared Ru−**3g** (1 mol %, S/C = 100), in 1 mL of H_2O and 0.5 mL of CH_2Cl_2 at 40 °C, unless otherwise noted. [b] The reactions were performed with 1 mmol of **1**, 5 equiv of HCOONa, 4 mol % of CTAB, and in situ prepared Ru−**3g** (0.5 mol %, S/C = 200), in 1 mL of H_2O at 40 °C. [c] With 0.2 mol % of Ru−**3g** (S/C = 500), 2.5 mmol of **1**, 5 equiv of HCOONa, 4 mol % of CTAB, in 2 mL of H_2O and 0.5 mL of CH_2Cl_2. [d] Isolated yield. [e] Determined by HPLC on a chiral column.

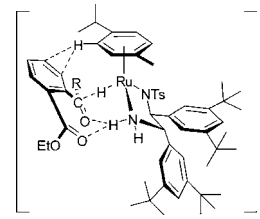


Figure 2. Proposed transition state.

In summary, a highly enantioselective asymmetric transfer hydrogenation of challenging 2-acylarylcarboxylates **1** has been successfully achieved in aqueous HCOONa by using a new diamine (TsDBuPEN, **3g**)/Ru(II) catalyst. The method offers a mild, facile, and practical access to a wide variety of 3-substituted phthalides in enantiomerically pure form. It represents one of the most efficient and general syntheses of highly optically active phthalides reported to date. Given the importance of chiral phthalides, this method should find potential applications in asymmetric synthesis and medicinal chemistry.

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Supporting Information Available: Explicit experimental details, including characterization data for chiral diamine ligands **3a**−**g**, phthalide products **2a**−**u**, and copies of HPLC and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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