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Rhodium-Catalyzed Highly Enantioselective Arylation of Cyclic Diketimines: Efficient Synthesis of Chiral Tetrasubstituted 1,2,5-Thiadiazoline 1,1-Dioxides

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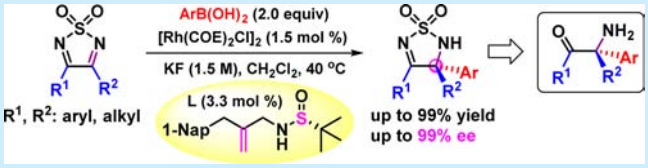
Supporting Information

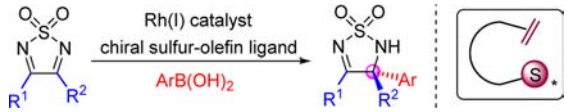
ABSTRACT: A highly enantioselective rhodium-catalyzed arylation of cyclic diketimines with arylboronic acids was achieved under mild conditions by employing a simple, sulfinamide-based branched olefin ligand. This protocol provides an efficient access to valuable chiral tetrasubstituted 1,2,5-thiadiazoline 1,1-dioxides in high yields with excellent enantioselectivities of up to 99% ee.



1,2,5-Thiadiazoline 1,1-dioxide derivatives are versatile building blocks for the synthesis of wide ranges of biologically active natural products and pharmaceutical compounds.[1] Moreover, as key precursors, they also provide efficient access to valuable cyclic sulfamides,[2] 1,2-diamines,[3] and α-amino acids.[4] Despite their great synthetic importance, however, stereoselective methods for preparing chiral thiadiazoline structures have been surprisingly limited.[5,6] Zezschwitz and co-workers recently reported a Ru-catalyzed asymmetric transfer hydrogenation approach in which one imine function of 3,4-disubstituted 1,2,5-thiadiazole 1,1-dioxides was selectively reduced to afford highly enantiomerically enriched thiadiazoline derivates, but it cannot be used for the construction of quaternary carbon stereocenters.[5] Accordingly, catalytic asymmetric 1,2-addition is robust and applicable for chiral tetrasubstituted thiadiazolines syntheses. However, there appears to be a significant challenge for the control of stereochemistry of additions to ketimine.[2d,3b,6−9] Until now there have been only several reports with specific thiadiazole substrates describing the successful use of transition-metal catalysts for this attractive transformation.[6] In 2012, Lam succeeded in the highly enantioselective addition of allyltrifluoroborates to simple 3-methyl-4-phenyl-1,2,5-thiadiazole 1,1-dioxide by use of a chiral Rh/diene catalyst.[6a] More recently, in another work by the Zhang group dealing with Pd-catalyzed enantioselective arylation of cyclic ketimines, a sole example of addition of 3,4-dimethyl-1,2,5-thiadiazole 1,1-dioxide with phenylboronic acid was described, giving the product with moderate enantioselectivity (84% ee).[6b] Thus, there is an unmet need for highly efficient asymmetric approaches that could enable easy access to versatile thiadiazoline derivatives in a stereospecific manner.

Previously, we have reported the design of a new and promising class of chiral sulfur-based olefin ligands and their successful applications in a series of Rh-catalyzed asymmetric reactions.[10−12] In particular, by employing a structurally simple chiral sulfinamide-based branched olefin as the ligand, the asymmetric 1,2-addition of stable, commercially available arylboronic acids to cyclic ketimines enables access to various α-quaternary benzosultams and benzosulfamidates with excellent enantioselectivities (up to 99% ee) under mild conditions.[11h,i] On the basis of these findings, we envisioned that these rhodium/sulfur−olefin complexes might also act as effective catalysts for the asymmetric addition to 3,4-disubstituted 1,2,5-thiadiazole 1,1-dioxides. Herein, we wish to disclose results of our efforts on the development of a mild catalytic asymmetric addition of 3,4-disubstituted 1,2,5-thiadiazole 1,1-dioxides for synthesis of various highly enantioenriched thiadiazolines (Scheme 1).

Scheme 1. Asymmetric Arylation of Cyclic Diketimines



Our initial investigation was carried out by evaluating the reaction of 3,4-diphenylthiadiazole[13] (**1a**) with *p*-tolylboronic acid (**2a**) under conditions similar to those previously reported for the asymmetric arylation of cyclic *N*-sulfonyl α-iminoester in the presence of optimal sulfur−olefin ligand.[11h] To our delight, the reaction proceeded very well and gave the expected α-quaternary thiadiazoline product **3a** in good yield (93%) with high enantioselectivity (94% ee) (Table 1, entry 1). Following up on this encouraging result, effects related to the reaction solvent, base, and temperature were carefully examined (entries 2−8). As summarized, of the solvents tested, CH_2Cl_2 exhibited the greatest preference in terms of enantiocontrol without loss of reactivity (92% yield, 97% ee) (entry 4). Employing other

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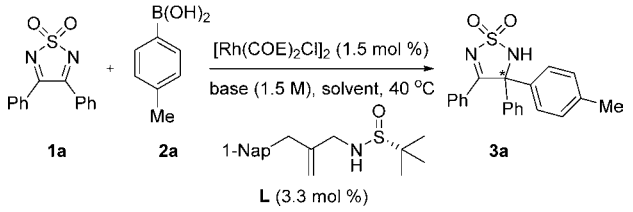
Table 1. Optimization of Reaction Conditions for Asymmetric 1,2-Addition of 1a with 2a[a]



entry	solvent	base	yield[b] (%)	ee[c] (%)
1	toluene	KF	93	94
2	THF	KF	72	94
3	CH_3OH	KF	23	95
4	CH_2Cl_2	KF	92	97
5	$ClCH_2CH_2Cl$	KF	93	95
6	CH_2Cl_2	K_3PO_4	33	96
7	CH_2Cl_2	KOH	15	97
8[d]	CH_2Cl_2	KF	80	97

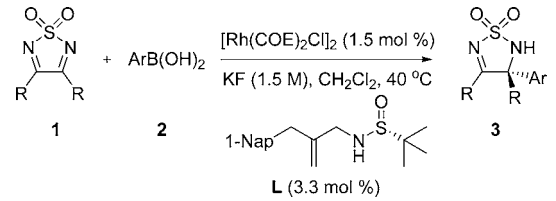
[a]The reaction was performed with **1a** (0.25 mmol), **2a** (0.5 mmol), $[Rh(COE)_2Cl]_2$ (1.5 mol %), **L** (3.3 mol %), and 1.0 equiv of base (1.5 M) in 1 mL of solvent at 40 °C for 6 h. COE = cyclooctene. [b]Isolated yields. [c]Determined by HPLC analysis using a chiral stationary phase. [d]The reaction was performed at room temperature.

bases, such as KOH or K_3PO_4, led to a dramatic decrease in the yield, which was due to competitive hydrolysis of the substrate (entries 6−7). In addition, performing the reaction at room temperature did not bring any noticeable change in the enantioselectivity, but a small erosion of yield was observed (entry 8).

Having identified the optimal reaction conditions, we sought to evaluate the scope and generality of the reaction. As revealed in Table 2, reactions involving various thiadiazoles **1** with a wide range of arylboronic acids **2** bearing diverse steric and electronic properties were all found to be successful, affording the corresponding thiadiazoline products **3** in high yields and excellent enantioselectivities (up to 99% ee). Generally, when R is aryl group, the electronic nature of the *para* and *meta* substituent on the phenyl ring of boronic acids did not appear to affect the reactivity and enantioselectivity (entries 1−19). With respect to sterically hindered arylboronic acids, such as 1-naphthylboronic acid or 3-thiopheneboronic acid, the reactions proceeded equally smoothly and gave products in up to 96% yield with outstanding stereocontrol (entries 9, 10, and 14). However, with the more hindered 2-methylphenylboronic acid, almost no reaction occurred. Furthermore, the electronically different *para*-substituted 3,4-diarylthiadiazole species **1b−d** and the less sterically hindered 3,4-dimethylthiadiazole **1e** are also proved to be suitable substrates, as they exhibited high reactivity and led to the formation of highly optically active C3 tetrasubstituted 1,2,5-thiadiazoline 1,1-dioxides **3k−u** (entries 11−21). Notably, in all the examined reactions, no diarylation occurs.

Further broadening of the substrate scope indicated that the reaction of arylboronic acids **2** with unsymmetrical thiadiazoles **4** could also proceed smoothly to provide the corresponding adducts **5** and **6** under the same reaction conditions (Scheme 2). Unlike the case of unsymmetrical α-diketones, regardless of differences in the steric and electronic properties of each imine moiety, the addition reaction performed with relatively low regioselectivity. Fortunately, in all cases, both regioisomers of the products could be readily separated from each other by

Table 2. Rh/L-Catalyzed Asymmetric Arylation of 1[a]



entry	R	Ar	3	yield[b] (%)	ee[c] (%)
1	C_6H_5 (**1a**)	4-MeC_6H_4	**3a**	92	97
2	C_6H_5 (**1a**)	4-$MeOC_6H_4$	**3b**	98	97
3	C_6H_5 (**1a**)	4-ClC_6H_4	**3c**	91	99
4	C_6H_5 (**1a**)	4-BrC_6H_4	**3d**	89	97
5	C_6H_5 (**1a**)	4-$CF_3C_6H_4$	**3e**	91	99
6	C_6H_5 (**1a**)	3-$MeOC_6H_4$	**3f**	88	98
7	C_6H_5 (**1a**)	3-ClC_6H_4	**3g**	89	99
8	C_6H_5 (**1a**)	2-naphthyl	**3h**	92	98
9	C_6H_5 (**1a**)	1-naphthyl	**3i**	94	99
10	C_6H_5 (**1a**)	3-thienyl	**3j**	96	98
11	4-BrC_6H_4 (**1b**)	4-MeC_6H_4	**3k**	87	98
12	4-BrC_6H_4 (**1b**)	4-ClC_6H_4	**3l**	84	99
13	4-BrC_6H_4 (**1b**)	4-FC_6H_4	**3m**	88	99
14	4-BrC_6H_4 (**1b**)	1-naphthyl	**3n**	85	99
15	4-MeC_6H_4 (**1c**)	4-$MeOC_6H_4$	**3o**	88	94
16	4-MeC_6H_4 (**1c**)	4-ClC_6H_4	**3p**	85	99
17	4-FC_6H_4 (**1d**)	4-MeC_6H_4	**3q**	91	98
18	4-FC_6H_4 (**1d**)	4-$MeOC_6H_4$	**3r**	99	96
19	4-FC_6H_4 (**1d**)	4-ClC_6H_4	**3s**	95	99
20	Me (**1e**)	4-$MeOC_6H_4$	**3t**	79	88
21	Me (**1e**)	4-ClC_6H_4	**3u**	70	96

[a]The reaction was performed with **1** (0.25 mmol), **2** (0.5 mmol), $[Rh(COE)_2Cl]_2$ (1.5 mol %), **L** (3.3 mol %), and 1.0 equiv of KF (1.5 M) in 1 mL of CH_2Cl_2 at 40 °C for 6 h. [b]Isolated yields. [c]Determined by HPLC analysis using a chiral stationary phase; see the Supporting Information for details.

standard column chromatography and obtained in moderate yields (up to 94% overall conversion). To our delight, the enantioselectivities remain essentially high (up to 97% ee).

Gratifyingly, the stereochemistry of the newly formed chiral center of product **3p** was determined to be *R* by X-ray crystallographic analysis. Assuming an analogous reaction mechanism, the same absolute configurations of the obtained thiadiazoline derivatives were assigned. Although the exact intermediate in catalytic process remains unclear at this time, an empirical transition-state model[14,15] is proposed. As depicted in Figure 1, the *tert*-butyl group provides an excellent stereo-environment, so the arylrhodium species formed by trans-metalation adopt a favorable conformation with the aryl group positioned *trans* to the olefin moiety of ligand. To avoid the steric interaction with the bulky R substituent, the thiadiazole substrate could coordinate only from the *re*-face of the imine C═N to form the major (*R*)-product, in accordance with the observed reaction stereochemical outcome.

Finally, the synthetic utility of the current method to prepare α-amino ketones containing a quaternary stereogenic center is shown in Scheme 3. Facile removal of the sulfonyl group by treatment of **3a** with hydrazine monohydrate at 110 °C gave the corresponding product **7** in 81% yield without loss of optical purity (96% ee). This protocol offers an efficient process for the synthesis of interesting optically active tertiary α-amino ketone derivatives.

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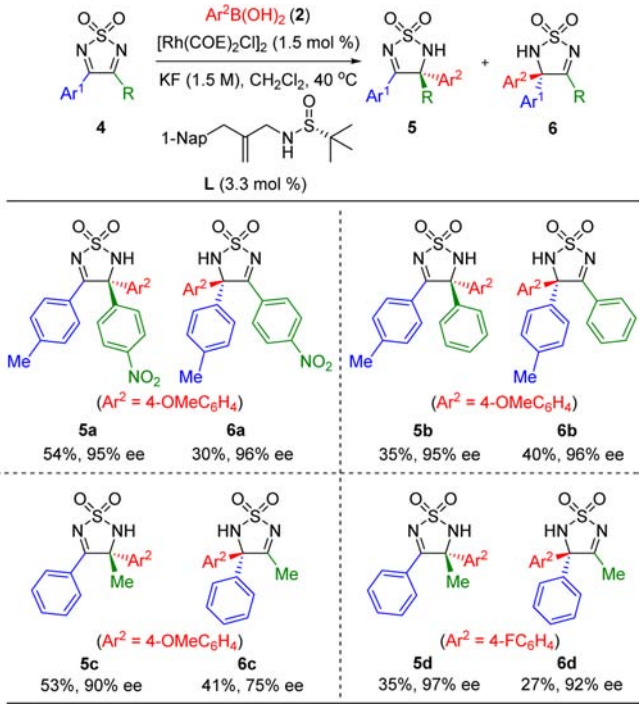
Scheme 2. Rh/L-Catalyzed Asymmetric Arylation of 4[a,b,c]



[a]The reaction was performed with **4** (0.25 mmol), **2** (0.5 mmol), $[Rh(COE)_2Cl]_2$ (1.5 mol %), **L** (3.3 mol %), and 1.0 equiv of KF (1.5 M) in 1 mL of CH_2Cl_2 at 40 °C for 6 h. [b]Isolated yields. [c]Determined by HPLC analysis a chiral stationary phase; see the Supporting Information for details.

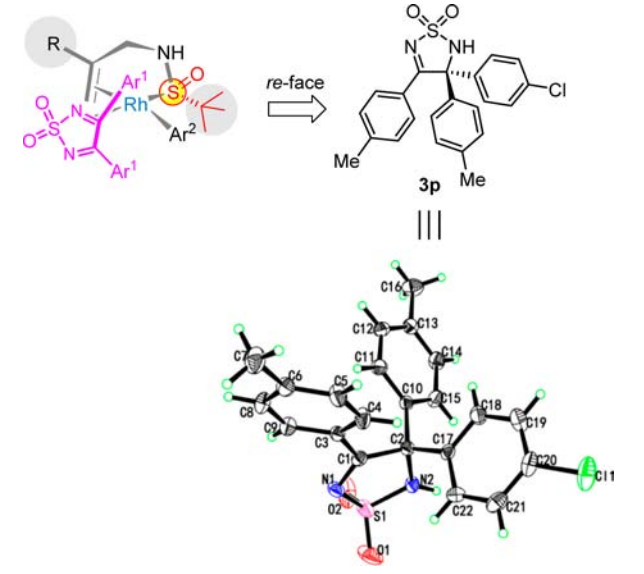


Figure 1. Proposed transition-state model and X-ray crystal structure of **3p**.

In summary, we have developed a highly efficient rhodium-catalyzed asymmetric arylation of 3,4-disubstituted thiadiazoles with arylboronic acids through the use of a simple branched chiral *N*-alkenylsulfinamide ligand. This approach provides direct access to synthetically important chiral quaternary carbon-containing 1,2,5-thiadiazoline 1,1-dioxide derivatives with substantial substitution diversity in high yields with excellent enantioselectivities (up to 99% ee) under exceptionally mild conditions. Following completion of the reaction, the arylation products could be easily converted to tertiary α-amino ketone compounds, which can be utilized as versatile chiral synthons in synthetic organic chemistry.

Scheme 3. Synthesis of the Tertiary α-Amino Ketones Derivative 7

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization, and crystallographic data for **3p** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Shum, P.; Gross, A.; Ma, L.; McGarry, D. G.; Merriman, G. H.; Rampe, D.; Ringheim, G.; Sabol, J. S.; Volz, F. A. US2005026916, 2005. (b) Ding, Q.; Graves, B. J.; Kong, N.; Liu, J.-J.; Lovey, A. J.; Pizzolato, G.; Roberts, J. L.; So, S.-S.; Vu, B. T.; Wovkulich, P. M. WO-2007063013, 2007. (c) Kawato, H.; Miyazaki, M.; Sugimoto, Y.; Naito, H.; Okayama, T.; Soga, T.; Uoto, K. WO-2008072665, 2008. (d) Uoto, K.; Kawato, H.; Sugimoto, Y.; Naito, H.; Miyazaki, M.; Taniguchi, T.; Aonuma, M. WO-2009151069, 2009. (e) Uoto, K.; Sugimoto, Y.; Naito, H.; Miyazaki, M.; Yoshida, K.; Aonuma, M. WO-2010082612, 2010.

(2) (a) Wright, J. B. *J. Org. Chem.* **1964**, *29*, 1905. (b) Rozas, M. F.; Piro, O. E.; Castellano, E. E.; Mirífico, M. V.; Vasini, E. J. *Molecules* **2000**, *5*, 503. (c) Lee, S. A.; Kwak, S. H.; Lee, K.-I. *Chem. Commun.* **2011**, *47*, 2372. (d) Nishimura, T.; Ebe, Y.; Fujimoto, H.; Hayashi, T. *Chem. Commun.* **2013**, *49*, 5504.

(3) (a) Pansare, S. V.; Rai, A. N.; Kate, S. N. *Synlett* **1998**, 623. (b) Hepburn, H. B.; Chotsaeng, N.; Luo, Y.; Lam, H. W. *Synthesis* **2013**, *45*, 2649.

(4) Lee, C.-H.; Korp, J. D.; Kohn, H. *J. Org. Chem.* **1989**, *54*, 3077.

(5) For an asymmetric reduction example, see: Schüttler, C.; Li-Böhmer, Z.; Harms, K.; Zezschwitz, P. V. *Org. Lett.* **2013**, *15*, 800.

(6) For asymmetric 1,2-addition examples, see: (a) Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 8309. (b) Yang, G.; Zhang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 7540.

(7) For recent related reviews, see: (a) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (b) Shibasaki, M.; Kanai, M. *Chem.*

Rev. **2008**, *108*, 2853. (c) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626.

(8) For selected examples of transition-metal-catalyzed enantioselective addition of carbon nucleophiles to acyclic ketimines: (a) Lauzon, C.; Charette, A. *Org. Lett.* **2006**, *8*, 2743. (b) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687. (c) Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 5530. (d) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168. (e) Shintani, R.; Takeda, M.; Soh, Y.-T.; Ito, T.; Hayashi, T. *Org. Lett.* **2011**, *13*, 2977.

(9) For selected examples of catalytic enantioselective addition of carbon nucleophiles to cyclic ketimines, see: (a) Nishimura, T.; Noishiki, A.; Tsui, G. C.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 5056. (b) Luo, Y.; Carnell, A. J.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 6762. (c) Nishimura, T.; Noishiki, A.; Ebe, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 1777.

(10) For related reviews, see: (a) Feng, X.; Du, H. *Asian J. Org. Chem.* **2012**, *1*, 204. (b) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95. For a focus review on chiral sulfur-olefin ligands in asymmetric catalysis, see: (c) Li, Y.; Xu, M.-H. *Chem. Commun.* **2014**, *50*, 3771.

(11) (a) Jin, S.-S.; Wang, H.; Xu, M.-H. *Chem. Commun.* **2011**, *47*, 7230. (b) Qi, W.-Y.; Zhu, T.-S.; Xu, M.-H. *Org. Lett.* **2011**, *13*, 3410. (c) Jin, S.-S.; Wang, H.; Zhu, T.-S.; Xu, M.-H. *Org. Biomol. Chem.* **2012**, *10*, 1764. (d) Zhu, T.-S.; Jin, S.-S.; Xu, M.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 780. (e) Wang, H.; Zhu, T.-S.; Xu, M.-H. *Org. Biomol. Chem.* **2012**, *10*, 9158. (f) Zhu, T.-S.; Chen, J.-P.; Xu, M.-H. *Chem.—Eur. J.* **2013**, *19*, 865. (g) Zhu, T.-S.; Xu, M.-H. *Chin. J. Chem.* **2013**, *31*, 321. (h) Wang, H.; Jiang, T.; Xu, M.-H. *J. Am. Chem. Soc.* **2013**, *135*, 971. (i) Wang, H.; Xu, M.-H. *Synthesis* **2013**, 2125. (j) Li, Y.; Zhu, D.-X.; Xu, M.-H. *Chem. Commun.* **2013**, *49*, 11659. For a focus review on sulfur−olefins, see ref 10c.

(12) For representative examples of using chiral sulfur−olefin ligands in asymmetric catalysis by other groups, see: (a) Thaler, T.; Guo, L.-N.; Steib, A. K.; Raducan, M.; Karaghiosoff, K.; Mayer, P.; Knochel, P. *Org. Lett.* **2011**, *13*, 3182. (b) Feng, X.; Wang, Y.; Wei, B.; Yang, J.; Du, H. *Org. Lett.* **2011**, *13*, 3300. (c) Chen, G.; Gui, J.; Li, L.; Liao, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7681. (d) Xue, F.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 7256.

(13) Coope, J. L.; Khan, M. G.; Moschner, K. F. US5753599, 1998.

(14) (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(15) Recent related computational studies: (a) Kantchev, E. A. B. *Chem. Commun.* **2011**, *47*, 10969. (b) Gosiewska, S.; Raskatov, J. A.; Shintani, R.; Hayashi, T.; Brown, J. M. *Chem.—Eur. J.* **2012**, *18*, 80. (c) Luo, Y.; Berry, N. G.; Carnell, A. J. *Chem. Commun.* **2012**, *48*, 3279.