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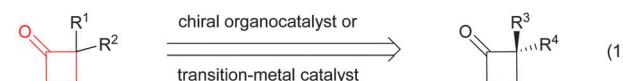
A highly diastereo- and enantioselective rhodium-catalyzed arylation of cyclobutenes for the efficient synthesis of chiral cyclobutanes has been developed. Chiral diene ligands exhibited excellent capability for the reaction diastereoselectivity control.

Chiral cyclobutanes exist as core subunits in numerous natural products^{1,2} and pharmaceutical agents.³ Moreover, a number of interesting chemical transformations associated with the four-membered strained ring render them valuable building blocks for organic synthesis.⁴ As a result, significant efforts have been directed to the asymmetric construction of chiral cyclobutane rings,⁵ and some catalytic asymmetric methods have been developed during the past decades, including asymmetric organo-⁶ or Lewis acid-catalyzed [2+2] cycloaddition,⁷ asymmetric ring expansion of cyclopropanes,⁸ asymmetric intramolecular ring closure of linear substrates⁹ and asymmetric functionalization of prochiral cyclobutane derivatives.^{10–12} The last strategy can avoid the relatively difficult construction of the constrained ring. More importantly, it provides a diverse synthetic approach using different functionalization reactions and easily accessible cyclobutanes as starting materials. To the best of our knowledge, almost all the present successful examples are limited to the chemical modifications of cyclobutanone substrates (Scheme 1, eqn (1)).¹⁰ Very recently, Yu and co-workers reported the asymmetric C–H activation/arylation of cyclobutane rings (eqn (2)).¹¹ Maulide and co-workers reported the palladium-catalyzed allylic alkylation of 4-chlorocyclobut-2-enecarboxylic acid (eqn (3)).¹² We envisioned that the well-established asymmetric rhodium-catalyzed addition of organometallic reagents to electron deficient double bonds could lead to a straightforward and diverse access to chiral cyclobutanes.¹³ Although five- and six-membered counterparts are among the

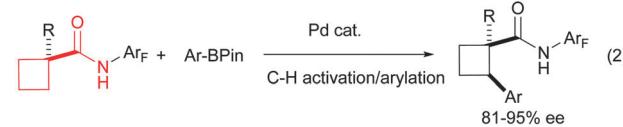
Synthesis of chiral cyclobutanes *via* rhodium/diene-catalyzed asymmetric 1,4-addition: a dramatic ligand effect on the diastereoselectivity[†]

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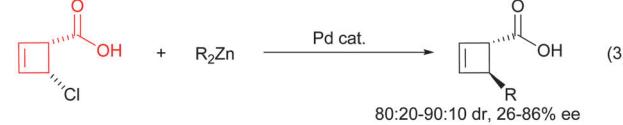
■ Asymmetric functionalization with cyclobutanone substrates



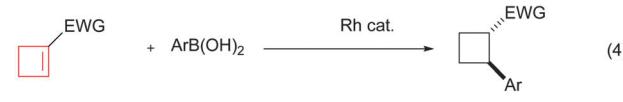
■ Enantioselective arylation of cyclobutanecarboxylic amide



■ Enantioselective allylic alkylation of cyclobutanecarboxylic acid



■ This work: rhodium-catalyzed arylation of cyclobutene substrates



- Easily accessible starting material
 - High enantioselectivity and diastereoselectivity

Scheme 1 Asymmetric functionalization of cyclobutane derivatives.

most tested substrates in rhodium-catalyzed 1,4-additions, only a single non-asymmetric example of the addition to cyclobutene was introduced by Tang and co-workers¹⁴ in their synthesis toward pipercyclobutanamide A and piperchabamide G and its asymmetric version remains unreported.

We reason that cyclobutene-1-carboxylate esters are suitable precursors for the enantioselective synthesis of chiral cyclobutanes, which can be easily prepared *via* three steps from widely available ethyl cyclobutanecarboxylate,¹⁵ and the ester groups could serve as a handle for further functionalization. However, it would be challenging to control both stereogenic centers generated in the addition process with such substrates. Especially, upon the first enantioselective addition at the β -position,

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Table 1 Rhodium-catalyzed 1,4-addition of phenylboronic acid to cyclobutene-1-carboxylates: effect of ester groups^a

Entry	Substrate (R)	Yield ^b (%)	trans/cis ^c	trans-3	ee of 3 ^d (%)
				3aa	21
1	1a (Et)	61	13/1	3aa	21
2	1b (iPr)	50	12/1	3ba	24
3	1c (tBu)	50	5/1	3ca	74
4	1d (Bn)	21	12/1	3da	9
5	1e (Ph)	25	15/1	3ea	74
6	1f (2,6-Me ₂ C ₆ H ₃)	80	2.6/1	3fa	87
7	1g (2,6-iPr ₂ C ₆ H ₃)	99	2.1/1	3ga	89
8	1h (2,6-Ph ₂ C ₆ H ₃)	35	12/1	3ha	92

^a Reactions were carried out with **1** (0.1 mmol), **2a** (0.2 mmol), [Rh(OH)(**L1**)]₂ (0.0015 mmol), 2.0 M aq. KOH (0.2 mmol) in toluene (1 mL) at 50 °C for 5 h. ^b A combined isolated yield of **3** and **4**.

^c Determined by GC analysis. ^d Determined by chiral HPLC analysis.

the subsequent protonation of the resulting oxa- π -allylrhodium intermediate would generate a second chiral center, which is usually quite difficult to control unless the α -substituent can induce a different protonation pathway in the reported similar examples.¹⁶ Herein, we report our research on the ligand enabled highly diastereo- and enantioselective rhodium-catalyzed arylation of cyclobutene-1-carboxylate esters for the efficient synthesis of chiral cyclobutanes.

First, we tested the addition of phenylboronic acid to the ethyl ester substrate (**1a**) in the presence of the active hydroxo rhodium complex [Rh(OH)(**L1**)].¹⁷ Gratifyingly, the reaction took place smoothly, affording the desired product in 61% yield with high diastereoselectivity despite low enantioselectivity. It was reported that the ester substituents could affect the stereoselectivity control for the aryl addition to linear α,β -unsaturated ester systems,¹⁸ thus a variety of different esters were examined in our case (Table 1). Although more sterically hindered substituents clearly improved the enantioselectivity, the reaction yield and diastereoselectivity were highly dependent on the structure pattern of substituents. The 2,6-diphenylphenyl substituent provided the highest enantioselectivity and maintained high diastereoselectivity, but a reduced reaction yield (entry 8).

Next, we turned to investigate this reaction using an *in situ* generated chiral rhodium catalyst. With ester **1h** as a substrate and [RhCl(C₂H₄)₂] as a precatalyst, a variety of chiral ligands were examined (Table 2).¹⁹ A significantly improved yield was obtained from the same ligand **L1** (entry 1 vs. Table 1, entry 8). However, attempts to further increase the enantioselectivity of this reaction by introducing different substituents to the phenyl ring of ligand **L1** were unsuccessful. It is worth mentioning that the diastereoselectivity was significantly improved by the introduction of electron-withdrawing substituents (entries 2–9). The highest diastereoselectivity was achieved using *para* 4-CF₃O substituted ligand **L8**, albeit with a slight loss in reaction yield, which was brought back by a lower temperature and a prolonged reaction time (entries 8 and 9). Bicyclo[2.2.2]octadiene **L9**²⁰ gave a similar reaction yield and diastereoselectivity

Table 2 Rhodium-catalyzed 1,4-addition of phenylboronic acid to cyclobutene-1-carboxylate **1h**: the effect of chiral ligands^a

Entry	Ligand	Yield ^b (%)	trans/cis ^c	ee of 3ha ^d (%)
			3ha	4ha
1	L1 (R = H)	97	15/1	92
2	L2 (R = 4-MeO)	77	11/1	89
3	L3 (R = 3,5-Me ₂)	73	9/1	93
4	L4 (R = 3,5-MeO ₂)	74	10/1	91
5	L5 (R = 4-F)	88	20/1	88
6	L6 (R = 4-CF ₃)	80	40/1	92
7	L7 (R = 3,5-F ₂)	75	47/1	92
8	L8 (R = 4-OCF ₃)	72	52/1	92
9 ^e	L8 (R = 4-OCF ₃)	99	62/1	92
10	L9	86	14/1	74
11	L10	8	2.2/1	—
12	L11	4	1.5/1	—
13	L12	1	1.6/1	—
14	L13	21	1.3/1	96
15	L14	5	1.5/1	—
16	L15	18	8/1	25
17	L16	3	25/1	—

^a Reactions were carried out with **1h** (0.1 mmol), **2a** (0.2 mmol), [Rh(C₂H₄)₂Cl]₂ (0.0015 mmol), **L** (0.0033 mmol), 2.0 M aq. KOH (0.2 mmol) in toluene (1 mL) at 50 °C for 5 h unless otherwise noted.

^b A combined yield of **3ha** and **4ha**, which was determined by GC using dodecane as an internal standard. ^c Determined by GC. ^d Determined by chiral HPLC analysis. ^e Reaction was made to run at 30 °C for 24 h.

compared with **L1**, but with lower enantioselectivity (entry 10). All the tested phosphine-containing ligands failed to promote this reaction effectively and only a trace amount of the product was generated in most cases under current reaction conditions (entries 11–17). Interestingly, while bisphosphine ligands gave low diastereoselectivities, relatively electron-deficient phosphoramidite ligands showed much higher diastereoselectivities, consistent with the trend observed for diene ligands. The high diastereoselectivity control by electron-deficient ligands may be attributed to the quick protonation of the carbon–rhodium bond, which was generated after the *cis* addition of the aryl rhodium species to the olefin. The stereochemically retentive direct protonation step could prevent the uncontrollable oxa- π -allylrhodium protonation pathway,²¹ thus the addition reaction led to the *trans* product.

With optimal reaction conditions identified (Table 2, entry 9), a wide range of arylboronic acids were explored as depicted in Table 3. Excellent diastereoselectivities were obtained for all the tested arylboronic acids although the reaction yields were affected by both steric and electronic properties of aryl groups.

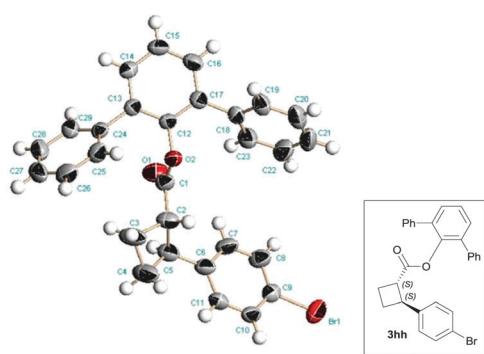


Table 3 Rhodium-catalyzed 1,4-addition of arylboronic acid to cyclobutene-1-carboxylate **1h**^a

Entry	Ar	<i>trans</i> -3	Yield ^b (%)	<i>trans/cis</i> ^c	ee ^d (%)
1	Ph (2a)	3ha	99	62/1	92
2	4-MeOC ₆ H ₄ (2b)	3hb	90	99/1	89
3	4- <i>t</i> BuC ₆ H ₄ (2c)	3hc	97	49/1	93
4	4-CF ₃ C ₆ H ₄ (2d)	3hd	73	32/1	98
5 ^e	4-CO ₂ MeC ₆ H ₄ (2e)	3he	36	>99/1	92
6	4-FC ₆ H ₄ (2f)	3hf	78	32/1	97
7	4-ClC ₆ H ₄ (2g)	3hg	96	49/1	97
8	4-BrC ₆ H ₄ (2h)	3hh	92	49/1	96
9	3-MeOC ₆ H ₄ (2i)	3hi	91	>99/1	93
10	3-FC ₆ H ₄ (2j)	3hj	84	49/1	97
11	3-CO ₂ MeC ₆ H ₄ (2k)	3hk	95	32/1	96
12 ^e	2-MeO (2l)	3hl	51	16/1	96
13	1-Naphthyl (2m)	3hm	96	>99/1	83
14	2-Naphthyl (2n)	3hn	68	>99/1	87

^a Reactions were carried out with **1h** (0.2 mmol), **2** (0.4 mmol), [Rh(C₂H₄)₂Cl]₂ (0.003 mmol), **L8** (0.0066 mmol), 2.0 M aq. KOH (0.4 mmol) in toluene (2 mL) at 30 °C for 24 h unless otherwise noted. ^b Isolated yield.

^c Determined by GC. ^d Determined by chiral HPLC analysis. ^e 50 °C.

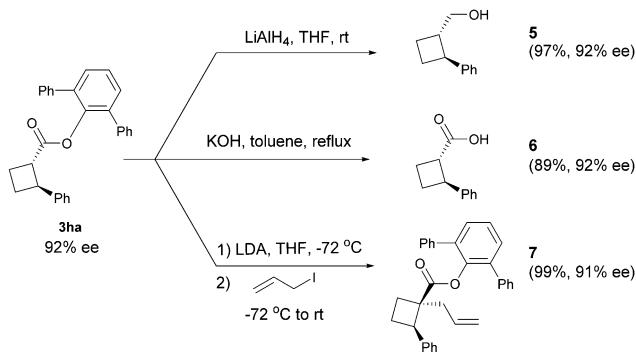


Scheme 2 The X-ray diffraction structure of **3hh**.

In general, electron-donating groups at the *para* position of the phenyl ring would benefit the reaction yields, and the sterically hindered *ortho*-substituted arylboronic acid gave only moderate reaction yield even at elevated reaction temperature. As for the enantioselectivity, the reactions with most arylboronic acids provided good to excellent ees (83–98%). The absolute configuration of product **3hh** was ambiguously determined by a single-crystal X-ray analysis as depicted in Scheme 2,²² and other products were assigned by analogy.

The obtained products can be easily converted to other cyclobutane derivatives. As shown in Scheme 3, reduction of ester **3ha** with LiAlH₄ at room temperature furnished alcohol **5** in 97% yield. The hydrolysis could provide acid **6** in 89% yield. Treatment of ester **3ha** with lithium diisopropylamide (LDA) followed by alkylation with allyl iodide afforded product **7** as a single diastereomer with a negligible loss in optical purity.

In summary, we have developed a highly diastereo- and enantioselective rhodium-catalyzed arylation of cyclobutene-1-carboxylate



Scheme 3 Transformations of product **3ha**.

esters, which provides an efficient synthetic approach for chiral butanes. Chiral diene ligands, especially electron deficient ones, exhibited excellent diastereoselectivity control. In addition, the versatile transformations of the product warrant the synthetic utility of this methodology.

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Notes and references

- For review: V. M. Dembitsky, *J. Nat. Med.*, 2008, **62**, 1–33.
- For selected examples: (a) P. S. Baran, D. P. O’Malley and A. L. Zografas, *Angew. Chem., Int. Ed.*, 2004, **43**, 2674–2677; (b) H. Ito, M. Hasegawa, Y. Takenaka, T. Kobayashi and K. Iguchi, *J. Am. Chem. Soc.*, 2004, **126**, 4520–4521; (c) K. Takao, N. Hayakawa, R. Yamada, T. Yamaguchi, H. Saegusa, M. Uchida, S. Samejima and K. Tadano, *J. Org. Chem.*, 2009, **74**, 6452–6461.
- For selected examples: (a) J. Singh, G. S. Bisacchi, S. Ahmad, J. D. Godfrey, Jr., T. P. Kissick, T. Mitt, O. Kocy, T. Vu, C. G. Papaioannou, M. K. Wong, J. E. Heikes, R. Zahler and R. H. Mueller, *Org. Process Res. Dev.*, 1998, **2**, 393–399; (b) P. Maity and B. König, *Biopolymers*, 2008, **90**, 8–27.
- For review: (a) J. C. Namyslo and D. E. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485–1537; (b) T. Seiser, T. Saget, D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2011, **50**, 7740–7752.
- For review: E. Lee-Ruff and G. Mladenova, *Chem. Rev.*, 2003, **103**, 1449–1483.
- (a) K. Ishihara and K. Nakano, *J. Am. Chem. Soc.*, 2007, **129**, 8930–8931; (b) G. Talavera, E. Reyes, J. L. Vicario and L. Carrillo, *Angew. Chem., Int. Ed.*, 2012, **51**, 4104–4107; (c) G.-J. Duan, J.-B. Ling, W.-P. Wang, Y.-C. Luo and P.-F. Xu, *Chem. Commun.*, 2013, **49**, 4625–4627.
- (a) T. A. Engler, M. A. Letavic, R. Iyengar, K. O. LaTessa and J. P. Reddy, *J. Org. Chem.*, 1999, **64**, 2391–2405; (b) E. Canales and E. J. Corey, *J. Am. Chem. Soc.*, 2007, **129**, 12686–12687; (c) S. Suárez-Pantiga, C. Hernández-Díaz, E. Rubio and J. M. González, *Angew. Chem., Int. Ed.*, 2012, **51**, 11552–11555.
- F. Kleinbeck and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 9178–9179.
- (a) R. Panish, S. R. Chintala, D. T. Boruta, Y. Z. Fang, M. T. Taylor and J. M. Fox, *J. Am. Chem. Soc.*, 2013, **135**, 9283–9286; (b) Y. X. Liu, Y. Liu, C. S. Shanahan, X. Xu and M. P. Doyle, *Org. Biomol. Chem.*, 2014, **12**, 5227–5234.
- (a) M. Lopp, A. Paju, T. Kanger and T. Pehk, *Tetrahedron Lett.*, 1996, **37**, 7583–7586; (b) D. Hazelard and A. Fadel, *Tetrahedron: Asymmetry*, 2005, **16**, 2067–2070; (c) D. Mailhol, M. M. Sanchez Duque, W. Raimondi, D. Bonne, T. Constantieux, Y. Coquerel and J. Rodriguez, *Adv. Synth. Catal.*, 2012, **354**, 3523–3532;



(d) D. J. Aitken, P. Caboni, H. Eijsberg, A. Frongia, R. Guillot, J. Ollivier, P. P. Piras and F. Secci, *Adv. Synth. Catal.*, 2014, **356**, 941–945; (e) C. M. Reeves, C. Eidamshaus, J. Kim and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2013, **52**, 6718–6721.

11 K.-J. Xiao, D. W. Lin, M. Miura, R.-Y. Zhu, W. Gong, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 8138–8142.

12 A. Misale, S. Niyomchon, M. Luparia and N. Maulide, *Angew. Chem., Int. Ed.*, 2014, **53**, 7068–7073.

13 For leading reviews on Rh-catalyzed asymmetric conjugated additions: (a) T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829–2844; (b) C. Gennari, C. Monti and U. Piarulli, *Pure Appl. Chem.*, 2006, **78**, 303–310; (c) J. Christoffers, G. Koripelly, A. Rosiak and M. Röessle, *Synthesis*, 2007, 1279–1300; (d) H. J. Edwards, J. D. Hargrave, S. D. Penrose and C. G. Frost, *Chem. Soc. Rev.*, 2010, **39**, 2093–2105.

14 R. Liu, M. Zhang, T. P. Wyche, G. N. Winston-McPherson, T. S. Bugni and W. Tang, *Angew. Chem., Int. Ed.*, 2012, **51**, 7503–7506.

15 (a) A. Campbell and H. N. Rydon, *J. Chem. Soc.*, 1953, 3002–3008; (b) J. C. Lee, K. A. Parker and N. S. Sampson, *J. Am. Chem. Soc.*, 2006, **128**, 4578–4579; (c) M. E. Jung and G. Deng, *J. Org. Chem.*, 2012, **77**, 11002–11005.

16 (a) T. Hayashi, T. Senda and M. Ogasawara, *J. Am. Chem. Soc.*, 2000, **122**, 10716–10717; (b) L. Navarre, S. Darses and J.-P. Genet, *Angew. Chem., Int. Ed.*, 2004, **43**, 719–723; (c) R. J. Moss, K. J. Wadsworth, C. J. Chapman and C. G. Frost, *Chem. Commun.*, 2004, 1984–1985; (d) L. Navarre, R. Martinez, J.-P. Genet and S. Darses, *J. Am. Chem. Soc.*, 2008, **130**, 6159–6169; (e) X. Zhang, G. Chen, P. Cao, J. Liu and J. Liao, *Tetrahedron Lett.*, 2012, **53**, 438–441.

17 (a) Z.-Q. Wang, C.-G. Feng, M.-H. Xu and G.-Q. Lin, *J. Am. Chem. Soc.*, 2007, **129**, 5336–5337; (b) S. Helbig, S. Sauer, N. Cramer, S. Laschat, A. Baro and W. Frey, *Adv. Synth. Catal.*, 2007, **349**, 2331–2337; (c) Z. Cui, H.-J. Yu, R.-F. Yang, W.-Y. Gao, C.-G. Feng and G.-Q. Lin, *J. Am. Chem. Soc.*, 2011, **133**, 12394–12397.

18 (a) J.-F. Paquin, C. R. J. Stephenson, C. Defieber and E. M. Carreira, *Org. Lett.*, 2005, **7**, 3821–3824; (b) T. Itoh, T. Mase, T. Nishikata, T. Iyama, H. Tachikawa, Y. Kobayashi, Y. Yamamoto and N. Miyaura, *Tetrahedron*, 2006, **62**, 9610–9621; (c) R. Shintani and T. Hayashi, *Org. Lett.*, 2011, **13**, 350–352.

19 Reviews of chiral olefin ligands: (a) C. Defieber, H. Grüetzmacher and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2008, **47**, 4482–4502; (b) J. B. Johnson and T. Rovis, *Angew. Chem., Int. Ed.*, 2008, **47**, 840–871; (c) R. Shintani and T. Hayashi, *Aldrichimica Acta*, 2009, **42**, 31–38; (d) C.-G. Feng, M.-H. Xu and G.-Q. Lin, *Synlett*, 2011, 1345–1356; (e) X. Feng and H. Du, *Asian J. Org. Chem.*, 2012, **1**, 204–213.

20 N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani and T. Hayashi, *J. Am. Chem. Soc.*, 2004, **126**, 13584–13585.

21 C. M. So, S. Kume and T. Hayashi, *J. Am. Chem. Soc.*, 2013, **135**, 10990–10993.

22 CCDC 1042990 contains the supplementary crystallographic data for compound **3hh**.

