Continuous Asymmetric Synthesis

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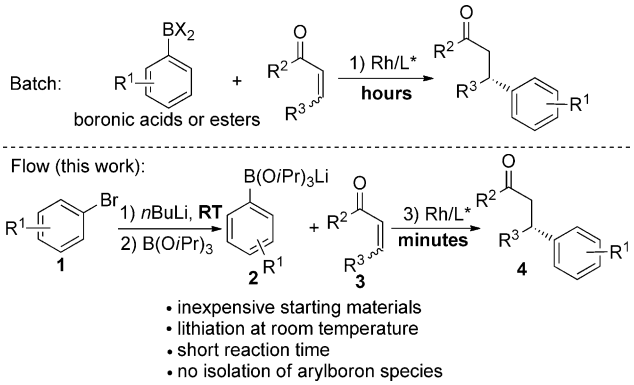
Enantioselective β-Arylation of Ketones Enabled by Lithiation/Borylation/1,4-Addition Sequence Under Flow Conditions**

*Wei Shu and Stephen L. Buchwald**

In the past decade, continuous flow methods have attracted much attention from both industry and academia due to their several well-defined advantages over batch procedures.[1,2] Recently, multistep synthesis in continuous flow has emerged as a powerful alternative to traditional procedures as it often allows one to circumvent time-consuming and labor-intensive isolation of intermediates.[3] Despite recent advances, multistep synthesis under flow conditions remains challenging due to its increased complexity as compared to single-step flow processes. Solvent and/or catalyst compatibility, flow rate synergy, as well as the effect of byproducts and impurities from upstream reactions on the downstream ones must be considered.[4] Additionally, the precipitation of solids is one of the biggest obstacles in the implementation of reactions into continuous flow, which often leads to irreversible blocking of the reactor. Although several techniques have been developed to address this problem, such as segmented liquid–liquid flow,[5] ultrasonication,[4a,6] and mechanical vibration,[7] the handling of solid in multistep continuous flow processes still remains a challenge.

Despite the many advantages associated with asymmetric catalysis,[8] reports of asymmetric catalysis under continuous flow conditions with good levels of enantioselectivity are still rare.[9,10] One reason might be that reactions in flow are usually conducted at elevated temperatures to decrease residence time, while most asymmetric catalytic methods are conducted at low temperatures.[11] Pioneered by Miyaura,[12] Hayashi,[12b,13] and Carreira,[14] the rhodium-catalyzed asymmetric 1,4-addition of boronic acids to α,β-unsaturated compounds is an important method for the construction of C–C bonds to afford enantioselective β-substituted carbonyl compounds.[15,16] Many arylboronic acids are, unfortunately, innately unstable, as well as expensive starting materials. Thus, we sought to develop a process that enabled the preparation of the requisite boron reagents in situ, followed by asymmetric 1,4-addition under flow conditions (Scheme 1). Herein, we report our success in developing the continuous rhodium-catalyzed asymmetric 1,4-addition, using lithium aryltriisopropylborates generated in a lithiation/borylation sequence.



Scheme 1. Three-step strategy for the synthesis of chiral β-arylated ketones under flow conditions.

Notably, this process is enabled by the efficient handling of solids under acoustic irradiation conditions. The use of a flow process allows for the rapid, safe and efficient lithiation of aryl bromides at room temperature, their conversion into aryl triisopropylborates, and subsequent utilization in rhodium-catalyzed asymmetric 1,4-addition.

We began our studies on the lithiation/borylation/1,4-addition sequence using the setup depicted in Figure 1 with 4-bromoanisole and 2-cyclohexenone **3a** as substrates. First, a solution of 4-bromoanisole (2.2 M in THF, 42 μL min^{-1}) was mixed with *n*BuLi (2.5 M in hexanes, 42 μL min^{-1}) using a T-mixer and introduced into a reactor (0.01 inch inner diameter, 2.6 cm of perfluoroalkoxyalkane (PFA) tubing) at room temperature. Under batch conditions, this reaction would require cryogenic temperatures and the slow addition of *n*BuLi. However, using flow conditions, the lithium–bromide

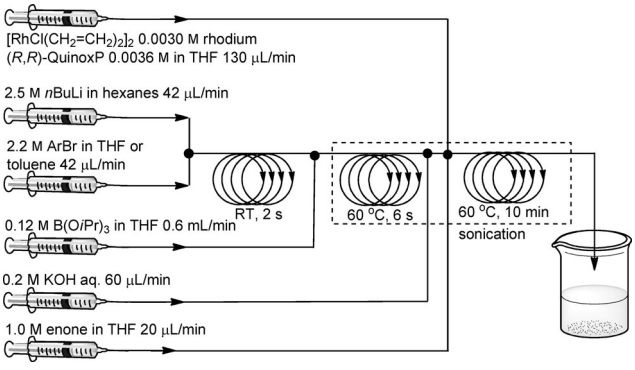


Figure 1. Continuous-flow setup for the lithiation/borylation/asymmetric 1,4-addition sequence.

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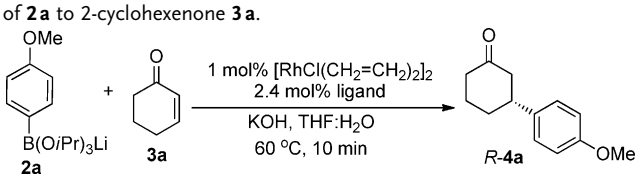
exchange was complete in 2 s, accompanied by a minimum amount of 4-*n*-butylanisole. Upon exiting the first reactor, the aryllithium was mixed with a stream of $B(OiPr)_3$ in THF before entering a second reactor, in which the lithium aryltriisopropylborate was generated. The reaction mixture was quenched by an aqueous solution of KOH (0.2 M, 60 μL min^{-1}), and then the combined solution was mixed with THF solutions of 2-cyclohexenone (1.0 M, 20 μL min^{-1}) and a catalyst (0.0030 M rhodium and 0.0036 M ligand, 130 μL min^{-1}). This combination was allowed to flow through a third reactor, after which, the product-containing solution was collected. The second and the third reactors were both submerged in a preheated 60 °C sonication bath to help mix the three phases of the reaction and prevent clogging. Due to the poor solubility of lithium triisopropyl(4-methoxyphenyl)-borate **2a**, the $B(OiPr)_3$ used must be dilute in order to prevent clogging. After testing several concentrations, we found that a 0.12 M solution of $B(OiPr)_3$ in THF could be successfully applied in this flow sequence.

Next, we tested various chiral ligands under biphasic conditions using the optimal lithiation/borylation conditions (Table 1). It was found that when bicyclo[2.2.2]octadiene-based chiral diene ligands **L1**[17] or **L2**[18] were used, **4a** was obtained in good yield with good enantioselectivity in 10 min (Table 1, entries 1 and 2). In contrast, the use of **L3**[19] gave the desired product **4a** in only 33 % yield (83 % *ee*) under the same conditions (Table 1, entry 3). Chiral phosphite ligands[20] (**L4** and **L5**) were not suitable for this reaction under biphasic conditions (Table 1, entries 4 and 5). The reaction was sluggish with biaryl-based chiral ligands (**L6** and **L7**),[12,21] despite **4a** being formed with good enantioselectivity (Table 1, entries 6 and 7). Employing (*R*,*R*)-1,2-bis-(4-methoxyphenyl)phenylphosphino)ethane (**L8**) gave racemic **4a** in 92 % yield (Table 1, entry 8). The best result was obtained with (*R*,*R*)-QuinoxP (**L9**)[22] as **4a** was produced in 96 % yield with 99 % *ee* in only 10 min (Table 1, entry 9). Interestingly, it has been reported that a lower *ee* (94 %) was obtained when a boronic acid was used with this ligand employing conventional procedures.[22]

We next examined the scope for this lithiation/borylation/rhodium-catalyzed asymmetric 1,4-addition sequence under flow conditions and the results are summarized in Table 2. The process could be successfully carried out with a variety of substituted aryl bromides containing either electron-donating or -withdrawing substituents. This circumvented the use of relatively expensive boronic acids,[23] and afforded the corresponding β-arylated products in good yields with excellent levels of enantioselectivity. Five-, six-, and seven-membered cyclic enones were all good substrates. In addition, acyclic enones with phenyl or aliphatic substituents were also efficiently transformed. Notably, even a small substituent, such as a methyl group at the β-position, also led to the desired product **4i** in 86 % yield with 93 % *ee*. Relatively hindered *ortho*-substituted aryl bromides also reacted in minutes to give the conjugate addition product **4j** in 91 % yield with 97 % *ee*.

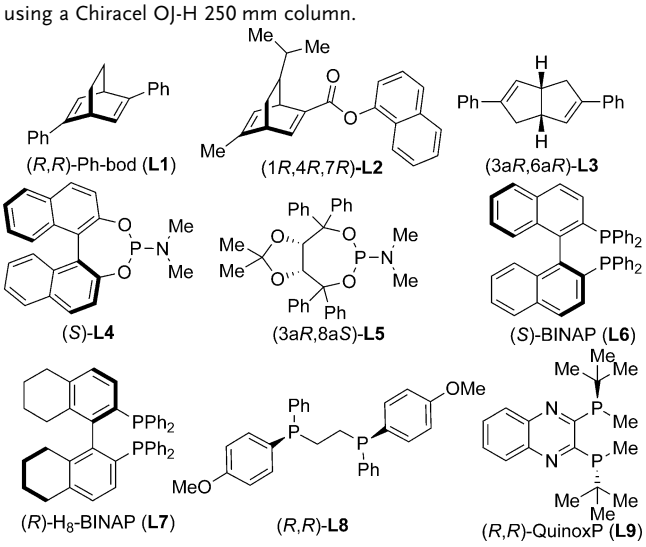
In summary, we have demonstrated an efficient three-step protocol for the synthesis of enantiopure β-arylated ketones in continuous flow under sonication conditions, representing the first example of a multistep asymmetric catalytic sequence in flow. Of importance is that this process uses readily available and inexpensive aryl bromides instead of arylboron reagents, operates at mild temperature and obviates the need for isolation or purification of intermediates. The protocol is quite general and can be accomplished in minutes. These features should render this process amenable to the synthesis of enantioenriched β-arylated ketones on large scale.

Table 1: Ligand effect on the rhodium-catalyzed asymmetric 1,4-addition of **2a** to 2-cyclohexenone **3a**.



Entry	Ligand	Yield of **4a** [%][a]	*ee* [%][b]
1	**L1**	83	96 (*R*)
2	**L2**	90	91 (*R*)
3	**L3**	33	83 (*S*)
4	**L4**	18	84 (*S*)
5	**L5**	–	–
6	**L6**	14	93 (*S*)
7	**L7**	19	95 (*R*)
8	**L8**	92	4 (*S*)
9	**L9**	96 (90)	99 (*R*)

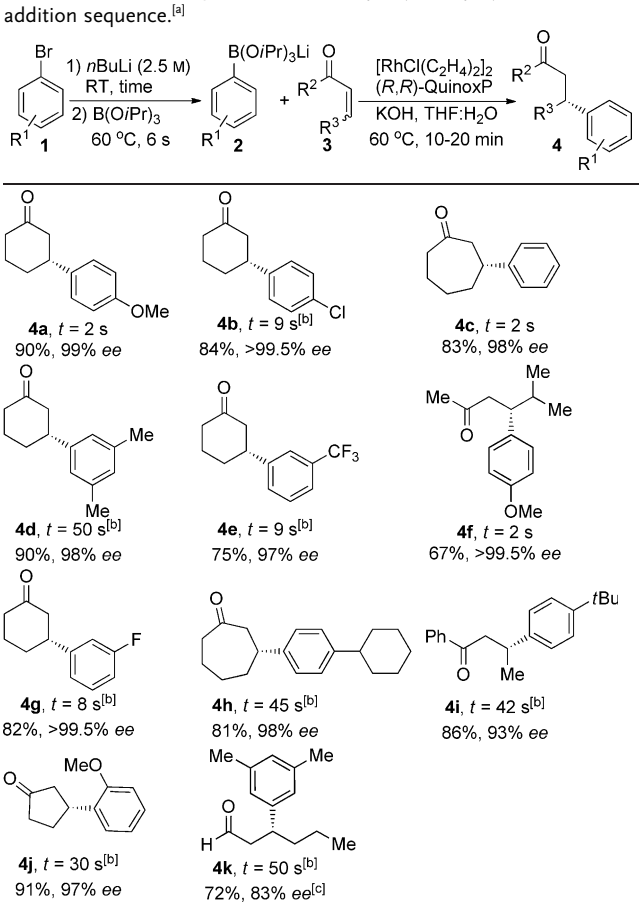
[a] GC yields based on **3a** with biphenyl as an internal standard. The number in the parenthesis is the yield of isolated product after flash chromatography. [b] The *ee* values were determined by HPLC analysis using a Chiracel OJ-H 250 mm column.



Experimental Section

General procedure: A THF solution of aryl bromide was loaded into a plastic syringe and a solution of *n*-butyllithium (2.5 M in hexanes) was loaded into a second plastic syringe. These two solutions were mixed at a T-mixer and delivered to the first microreactor made of PFA (perfluoroalkoxyalkane) tubing (0.01–0.04 inch inner diameter) using a Harvard Apparatus syringe pump. A second syringe pump was used to deliver a solution of $B(OiPr)_3$ (0.12 M in THF), and it was mixed with the stream exiting the first reactor at a second T-mixer. The combined stream was introduced into the second microreactor

Table 2: Substrate scope of the lithiation/borylation/asymmetric 1,4-addition sequence.[a]



[a] Yields of isolated products based on **3**. The *ee* values were determined by HPLC analysis unless otherwise stated. [b] A solution of the aryl bromide in toluene was used for the lithiation reaction. [c] The *ee* value was determined by chiral GC.

(PFA tubing, 1/16 inch inner diameter). The base solution was loaded into a fourth plastic syringe and pumped into the system using a third Harvard Apparatus syringe pump. Sequentially, the solution of α,β-unsaturated carbonyl compound as well as the solution of $[RhCl(CH_2{=}CH_2)_2]_2$ and (*R*,*R*)-QuinoxP in THF were loaded into a fifth and a sixth plastic syringes, which were merged with the combined stream of base solution and the mixture from the second reactor using a fourth and a fifth Harvard Apparatus syringe pumps. The combined mixture was introduced into the third microreactor (PFA tubing, 0.062 inch inner diameter). Upon exiting the reactor, the mixture was collected. Further details on the flow setup and workup procedures can be found in Supporting Information.

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[1] For selected reviews on flow chemistry, see: a) T. Noël, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010; b) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, *47*, 4583; c) C. Wiles, P. Watts, *Chem. Commun.* **2011**, *47*, 6512; d) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675; e) C. G. Frost, L. Mutton, *Green Chem.* **2010**, *12*, 1687; f) A. Cukalovic, J. C. M. R. Monbaliu, C. V. Stevens, *Top. Heterocycl. Chem.* **2010**, *23*, 161; g) R. L. Hartman, K. F. Jensen, *Lab Chip* **2009**, *9*, 2495; h) K. Geyer, T. Gustafsson, P. H. Seeberger, *Synlett* **2009**, 2382; i) J.-i. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450; j) T. Fukuyama, M. T. Rahman, M. Sata, I. Ryu, *Synlett* **2008**, 151; k) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300; l) A. Kirschning, W. Solodenko, K. Mennecke, *Chem. Eur. J.* **2006**, *12*, 5972; m) K. Geyer, J. D. C. Codée, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8434; n) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem.* **2004**, *116*, 410; *Angew. Chem. Int. Ed.* **2004**, *43*, 406.

[2] a) Y.-i. Yoshida, *Flash Chemistry: Fast Organic Synthesis in Microsystems*, Wiley-Blackwell, Hoboken, **2008**; b) T. Wirth, *Microreactors in Organic Synthesis and Catalysis*, Wiley-VCH, Weiheim, **2008**; c) P. H. Seeberger, T. Blume, *New Avenues to Efficient Chemical Synthesis-Emerging Technologies*, Springer, Berlin, **2007**; d) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH, Weiheim, **2000**.

[3] a) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17; b) C. Wiles, P. Watts, *Micro Reaction Technology in Organic Synthesis*, Taylor & Francis, New York, **2011**.

[4] a) W. Shu, L. Pellegatti, M. A. Oberli, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 10853; *Angew. Chem. Int. Ed.* **2011**, *50*, 10665; b) P. Li, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 6520; *Angew. Chem. Int. Ed.* **2011**, *50*, 6396; c) T. Noël, S. Kuhn, A. J. Musacchio, K. F. Jensen, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 6065; *Angew. Chem. Int. Ed.* **2011**, *50*, 5943; d) W. Shu, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 2321; e) L. Malet-Sanz, J. Madrzak, S. V. Ley, I. R. Baxendale, *Org. Biomol. Chem.* **2010**, *8*, 5324; f) M. D. Hopkin, I. R. Baxendale, S. V. Ley, *Chem. Commun.* **2010**, *46*, 2450; g) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi, J.-i. Yoshida, *Angew. Chem.* **2010**, *122*, 7705; *Angew. Chem. Int. Ed.* **2010**, *49*, 7543; h) A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. T. McQude, *Angew. Chem.* **2009**, *121*, 8699; *Angew. Chem. Int. Ed.* **2009**, *48*, 8547; i) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem.* **2009**, *121*, 4077; *Angew. Chem. Int. Ed.* **2009**, *48*, 4017.

[5] a) H. Song, D. L. Chen, R. F. Ismagilov, *Angew. Chem.* **2006**, *118*, 7494; *Angew. Chem. Int. Ed.* **2006**, *45*, 7336; b) S. L. Poe, M. A. Cummings, M. P. Haaf, D. T. McQuade, *Angew. Chem.* **2006**, *118*, 1574; *Angew. Chem. Int. Ed.* **2006**, *45*, 1544; c) I. Shestopalov, J. D. Tice, R. F. Ismagilov, *Lab Chip* **2004**, *4*, 316.

[6] a) T. Horie, M. Sumino, T. Tanaka, Y. Matsushita, T. Ichimura, J.-i. Yoshida, *Org. Process Res. Dev.* **2010**, *14*, 405; b) J. Sedelmeier, S. V. Ley, I. R. Baxendale, M. Baumann, *Org. Lett.* **2010**, *12*, 3618; c) T. Noël, J. R. Naber, R. L. Hartman, J. P. McMullen, K. F. Jensen, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 287; d) R. A. Maurya, P. H. Hoang, D.-P. Kim, *Lab Chip* **2012**, *12*, 65.

[7] S. J. Dolman, J. L. Nyrop, J. T. Kuethe, *J. Org. Chem.* **2011**, *76*, 993.

[8] E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis I–III*, Springer, Berlin, **1999**.

[9] X. Y. Mak, P. Laurino, P. H. Seeberger, *Beilstein J. Org. Chem.* **2009**, *5*, 19, and references therein.

[10] a) M. A. Pericàs, C. I. Herrerías, L. Solà, *Adv. Synth. Catal.* **2008**, *350*, 927; b) D. Popa, R. Marcos, S. Sayalero, A. Vidal-Ferran, M. A. Pericàs, *Adv. Synth. Catal.* **2009**, *351*, 1539; c) J. Rolland, X. C. Cambeiro, C. Rodríguez-Escrich, M. A. Pericàs, *Beilstein J. Org. Chem.* **2009**, *5*, 56; d) K. Takeda, T. Oohara, N. Shimada, H. Nambu, S. Hashimoto, *Chem. Eur. J.* **2011**, *17*, 13992; e) C. Ayats, A. H. Henseler, M. A. Pericàs, *ChemSusChem* **2012**, *5*, 320.

[11] A. Odedra, P. H. Seeberger, *Angew. Chem.* **2009**, *121*, 2737; *Angew. Chem. Int. Ed.* **2009**, *48*, 2699.

[12] a) M. Sakai, H. Hayashi, N. Miyaura, *Organometallics* **1997**, *16*, 4229; b) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579.

[13] a) Y. Takaya, M. Ogasawara, T. Hayashi, *Tetrahedron Lett.* **1999**, *40*, 6957; b) T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052; c) A. Kina, H. Iwamura, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 3904; d) A. Kina, Y. Yasuhara, T. Nishimura, H. Iwamura, T. Hayashi, *Chem. Asian J.* **2010**, *5*, 707.

[14] C. Fischer, C. Defieber, T. Suzuki, E. M. Carreira, *J. Am. Chem. Soc.* **2004**, *126*, 1628.

[15] For recent reviews on rhodium-catalyzed asymmetric 1,4-addtion, see: a) P. Tian, H.-Q. Dong, G.-Q. Lin, *ACS Catal.* **2012**, *2*, 95; b) H. J. Edwards, J. D. Hargrave, S. D. Penrose, C. G. Frost, *Chem. Soc. Rev.* **2010**, *39*, 2093; c) R. Shintani, T. Hayashi, *Aldrichimica Acta* **2009**, *42*, 31; d) C. Defieber, H. Grützmacher, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 4558; *Angew. Chem. Int. Ed.* **2008**, *47*, 4482; e) J. B. Johnson, T. Rovis, *Angew. Chem.* **2008**, *120*, 852; *Angew. Chem. Int. Ed.* **2008**, *47*, 840.

[16] a) G. Berthon, T. Hayashi in *Catalytic Asymmetric Conjugate Reactions* (Ed.: A. Córdova), Wiley-VCH, Weinheim, **2010**, chap. 1; b) R. Shintani, T. Hayashi in *New Frontiers in Asymmetric Catalysis* (Eds.: K. Mikami, M. Lautens), Wiley, Hoboken, **2007**, chap. 3; c) K. Yoshida, T. Hayashi in *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**, chap. 4; d) K. Yoshida, T. Hayashi in *Modern Rhodium-Catalyzed Organic Reactions* (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**, chap. 3.

[17] a) N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 13584; b) Y. Otomaru, K. Okamoto, R. Shintani, T. Hayashi, *J. Org. Chem.* **2005**, *70*, 2503.

[18] R. Shintani, Y. Tsutsumi, M. Nagaosa, T. Nishimura, T. Hayashi, *J. Am. Chem. Soc.* **2009**, *131*, 13588.

[19] a) Z.-Q. Wang, C.-G. Feng, M.-H. Xu, G.-Q. Lin, *J. Am. Chem. Soc.* **2007**, *129*, 5336; b) S. Helbig, S. Sauer, N. Cramer, S. Laschat, A. Baro, W. Frey, *Adv. Synth. Catal.* **2007**, *349*, 2331.

[20] A. Duursma, J.-G. Boiteau, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2004**, *69*, 8045.

[21] a) A. Kina, Y. Yasuhara, T. Nishimura, H. Iwamura, T. Hayashi, *Chem. Asian J.* **2010**, *5*, 707; b) F. Le Boucher d'Herouville, A. Millet, M. Scalone, V. Michelet, *J. Org. Chem.* **2011**, *76*, 6925.

[22] T. Imamoto, K. Sugita, K. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11934.

[23] For selected examples on the cost of aryl bromides vs. corresponding arylboronic acids according to the largest package available in Aldrich: 1-bromo-4-chlorobenzene (0.09$/g) vs. 4-chlorophenylboronic acid (7.26$/g); 3-bromobenzotrifluoride (0.56$/g) vs. 3-(trifluoromethyl)phenylboronic acid (35.4$/g).

[24] a) M. Ueda, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 4450; b) S. Oi, M. Moro, H. Ito, Y. Honma, S. Miyano, Y. Inoue, *Tetrahedron* **2002**, *58*, 91.

Communications

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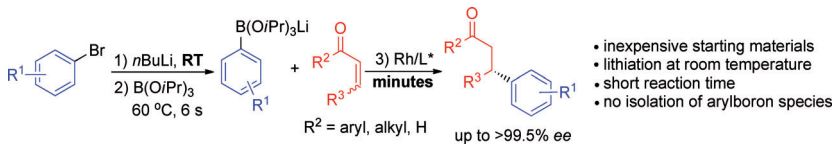
Enantioselective β-Arylation of Ketones Enabled by Lithiation/Borylation/1,4-Addition Sequence Under Flow Conditions



The first multistep asymmetric catalysis in flow has been realized using a lithiation/borylation/rhodium-catalyzed 1,4-addition sequence. The three-step sequence starts from readily available and inexpensive aryl bromides, affording β-arylated ketones in good yields with high levels of enantioselectivity.