Organic LETTERS

Letter

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Heteroarylboronates in Rhodium-Catalyzed 1,4-Addition to Enones

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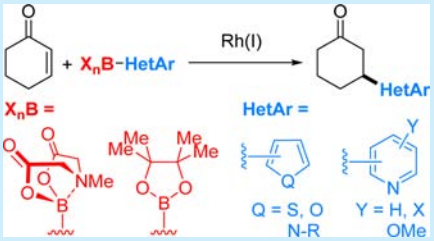
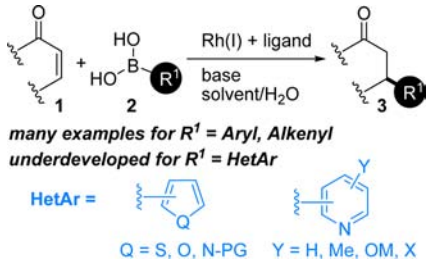
Supporting Information

ABSTRACT: Rhodium(I)-catalyzed 1,4-addition of aryl and alkenylboronic acids to α,β-unsaturated carbonyl compounds is well established, but the transfer of heteroaryl residues in this reaction remains underdeveloped. We have studied heteroaryl MIDA and pinacol boronates as alternatives to the labile boronic acid counterparts. Under racemic conditions, 12 adducts with heteroaryl residues, among them unsubstituted 3- and 4-pyridinyl, 2-furanyl, thienyl, and pyrrolyl groups, were obtained in moderate to excellent yields. The enantioselective version of the reaction proved highly sensitive to the electronic character of the heteroaryl substituents, with boronates carrying electron-rich residues giving modest to high yields but consistently high enantiomeric excesses.



Rhodium(I)-catalyzed 1,4-addition of boronic acids (**2**) to α,β-unsaturated carbonyl compounds (**1**) has emerged as a powerful tool for C−C bond formation under the setup of a new stereocenter.[1,2] While the reaction is well-documented for aryl and alkenylboronic acids, there are few examples for the transfer of heteroaryl residues[3] (Scheme 1). This is due to the lability of heteroarylboronic acids,[4] resulting in rapid protodeboration[5] under the aqueous basic conditions of rhodium-mediated 1,4-additions. Therefore, alternative reagents have to be sought.

Scheme 1. Scope for Rhodium-Catalyzed 1,4-Additions



Recently, Frost[6] and Martin[7] reported asymmetric 1,4-addition of heteroarylzinc and titanium reagents under anhydrous conditions, but these organometallics are highly sensitive and not commercially available, rendering this approach inconvenient. A more attractive alternative is to replace heteroarylboronic acids with stabilized boronate reagents, e.g. pinacol boronates (**4**), trifluoroborates[8] (**5**), cyclic triol borates[9] (**6**), or *N*-methylimino diacetic acid (MIDA) boronates[10] (**7**) (Figure 1). These compounds continuously generate boronic acids under basic aqueous conditions and are highly successful in Suzuki−Miyaura reactions,[11] but there are surprisingly few examples for heteroarylboronates in rhodium-catalyzed 1,4-additions.

Aryl pinacol boronates are well-known in 1,4-additions,[12] but only a few heteroaryl derivatives have been studied.[13]

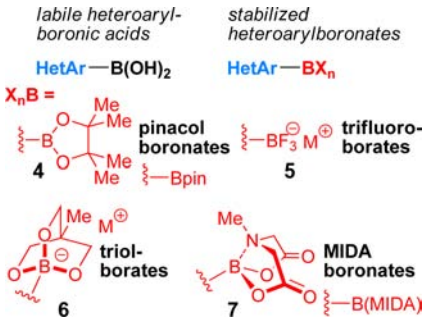


Figure 1. Heteroarylboronates as alternatives to boronic acids.

Trifluoroborates were reported in racemic and stereoselective 1,4-additions by Batey[14] and Genêt,[15] but successful heteroaryl examples are restricted to the 3-thienyl group. Studies on heteroaryl triolborates were performed by Miyaura.[16] With these, asymmetric 1,4-addition of 2-furanyl groups[16b] and methoxy-substituted 2-thienyl as well as 3- and 2-pyridinyl residues was successful, while the reaction failed without additional electron-donating substituents on the heteroaryl cores.[16a]

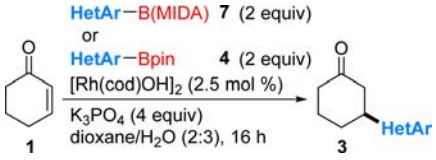
MIDA boronates were introduced to Suzuki−Miyaura couplings by Burke,[17] and currently, they are the reagents of choice for the transfer of heteroaryl residues in this cross-coupling reaction, which also requires aqueous basic conditions.[10] Surprisingly, there are no reports on heteroaryl MIDA boronates in 1,4-additions; to the best of our knowledge, only aryl[18] and alkenyl[19] MIDA boronates have been employed for this transformation.[20] Our group has introduced new carbohydrate-derived olefin ligands for stereoselective rhodium-catalyzed 1,4-addition,[21−24] and in the course of this work, we became interested in studying the reaction of heteroaryl-boronates in more detail.

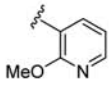
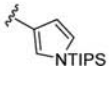
Received: September 4, 2014
Published: September 25, 2014

dx.doi.org/10.1021/ol502630w | *Org. Lett.* 2014, 16, 5212−5215

As many MIDA boronates (**7**) and pinacol boronates (**4**) with heteroaryl groups are commercially available, we performed our investigation on racemic 1,4-additions to cyclohexenone (**1**) with these substrates (Table 1). Using $[Rh(cod)OH]_2$ (cod: 1,5-cyclooctadiene) as the catalyst and phenyl MIDA boronate (**7a**) as a model substrate, we set out to develop suitable reaction conditions. After extensive optimization, K_3PO_4 (4 equiv) as the base, a 2:3 mixture of dioxane and water, and a reaction temperature of 60 °C were identified as optimal, giving adduct **3a** in high yield (entry 1). With these optimized conditions, we started our study on heteroaryl MIDA boronates.

Table 1. Racemic 1,4-Addition of Heteroaryl MIDA and Pinacol Boronates to Cyclohexenone



	boronate **7** or **4** HetAr		temp [°C]	product **3**	yield [%][a]
1[b]		**7a**	60	**3a**	91
2		**7b**	60	**3b**	71
3		**7c**	60	**3c**	90
4		**7d**	60	**3d**	88
5		**7e**	60	**3e**	46
6		**7f**	60	**3f**	42
7		**7f**	rt		-
8		**4f**	60		73
9		**7g**	rt	**3g**	-
10		**7h**	60	**3h**	85
11		**4h**	60		31
12		**7i**	60	**3i**	34
13		**7i**	rt		74
14[c]		**4i**	rt		95
15		**7j**	rt	**3j**	24
16		**4j**	rt		30
17		**7k**	rt	**3k**	36
18		**4k**	rt		32
19		**7m**	60	**3m**	75
20		**4n**	rt	**3n**	99
21[c]		**4o**	rt	**3o**	99

[a]Isolated yield after chromatography. [b]Reaction with 1.5 mol % $[Rh(cod)OH]_2$. [c]The pinacol boronate was added via syringe pump.

As the first example, we investigated 3-thienyl MIDA boronate **7b**. Most known examples of heteroaryl transfer in 1,4-additions involve the 3-thienyl residue,[3a,b,13−16] and indeed, the reaction with **7b** proceeded smoothly (entry 2). Pyridinylboronic acids are known for their lability,[4] and so far pyridinyl triol borates with additional electron-donating substituents on the pyridine core were the only successful substrates.[16a] Therefore, we were very pleased to find that, apart from activated 3-pyridinyl derivative **7c**, 3-pyridinyl MIDA boronates **7d** and **7e** with chloro and fluoro substitution as well as derivative **7f** carrying an unsubstituted pyridinyl group also gave the expected products (entries 3−6). Yields were strongly dependent on the electronic makeup of the 3-pyridinyl residue, with 90% for methoxy derivative **7c** and 88% for chloro derivative **7d**, but yields <50% were obtained for the addition products of fluorinated and unsubstituted 3-pyridinyl MIDA boronates **7e** and **7f**. An attempt to improve the yield for **7f** by performing the reaction at rt resulted in no conversion (entry 7). Therefore, we repeated the experiment with 3-pyridinyl pinacol boronate **4f** as an alternative reagent at 60 °C, which led to a substantially improved yield of 73% (entry 8). Boron reagents with unsubstituted 2-pyridinyl groups are notorious for their low stability,[4] and unfortunately, MIDA derivative **7g** failed to yield any product (entry 9). 4-Pyridinyl MIDA and pinacol boronates **7h** and **4h** produced **3h** in 85% and 31% yield, respectively (entries 10, 11); in a related study, the corresponding boronic acid led to a very modest yield.[3d]

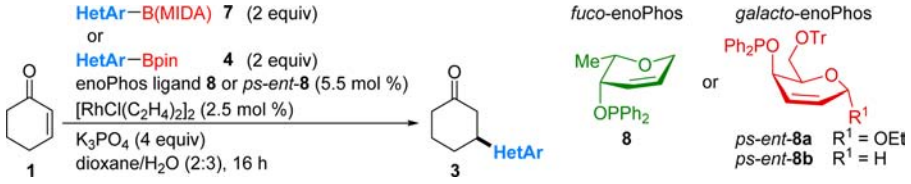
Next, we turned our attention to unsubstituted five-membered heteroarenes. At 60 °C, 3-furanyl MIDA derivative **7i** gave product **3i** in moderate yield, but reactions with **7i** or pinacol boronate **4i** at rt led to greatly improved results (entries 12−14).

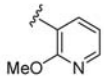
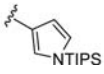
Unsubstituted 2-furanyl-, thienyl-, and pyrrolylboronates are challenging substrates,[4] and so far, there are only a few reports concerning 2-thienyl[3c] and furanyl[16b] residues. At rt, 2-thienyl MIDA boronate **7j** and pinacol boronate **4j** gave **3j** in moderate yield (entries 15, 16). Similar results were obtained for 2-furanyl derivatives **7k** and **4k** (entries 17, 18). In contrast, *N*-Boc 2-pyrrolyl MIDA boronate **7m** produced **3m** in high yield, and more electron-rich *N*-methyl 2-pyrrolyl pinacol boronate **4n** even gave 99% of **3n** (entries 19, 20). The same excellent yield was obtained with 3-pyrrolyl boronate **4o**[25] (entry 21).

After the encouraging results of the racemic study, we set out to develop an asymmetric protocol. As a catalyst system we chose $[RhCl(C_2H_4)_2]_2$ in the presence of *fuco*-enoPhos (**8**) or *galacto*-enoPhos (*ps-ent*-**8**) (Table 2). Both chiral ligands are accessible from inexpensive monosaccharides[23,24] and act as *pseudo* enantiomers in 1,4-additions of arylboronic acids.[24] In the presence of the rhodium complex with *fuco*-ligand **8**, and under otherwise unchanged conditions, phenyl MIDA boronate **7a** smoothly gave adduct **3a** as the expected (*R*)-enantiomer[24] in high yield and excellent ee (entry 1). Reaction of 3-thienyl MIDA derivative **7b** in the presence of **8** at 60 °C yielded 65% of (*R*)-**3b** in 91% ee, while *galacto*-ligand *ps-ent*-**8b** produced the (*S*)-enantiomer in 56% yield and 96% ee (entries 2, 3). At rt, the yield and stereoselectivity improved for the reaction with

dx.doi.org/10.1021/ol502630w | Org. Lett. 2014, 16, 5212−5215

Table 2. Asymmetric 1,4-Addition of Heteroaryl MIDA Boronates and Pinacol Boronates to Cyclohexenone



entry	boronate 7 or 4 HetAr		enoPhos ligand	temp [°C]		product 3 yield [%][a]	ee [%][b]
1[c]		7a	8	60	3a	88	97 (*R*)
2			8	60		65	91 (*R*)
3		7b	*ps-ent*-8b	60	3b	56	96 (*S*)
4			8	rt		77	**95** (*R*)
5			*ps-ent*-8b	rt		56	**98** (*S*)
6			8	60		33	**90** (+)
7		7c	*ps-ent*-8a	60	3c	44	**94** (-)
8[d]			8	rt		80	**95** (+)
9			*ps-ent*-8a	rt		37	**97** (-)
10		7i	8			24	**91** (+)
11		7i	*ps-ent*-8b	rt	3i	19	**93** (-)
12		4i	8			37	**89** (+)
13		7j	8			15	**90** (-)
14		7j	*ps-ent*-8b	rt	3j	10	**95** (+)
15		4j	8			11	**93** (-)
16		7k	8			14	81 (-)
17		7k	*ps-ent*-8b	rt	3k	16	**90** (+)
18		4k	8			19	71 (-)
19		4n	8	rt	3n	81	82 (+)
20[e]		4o	*ps-ent*-8b	rt	3o	56	**94** (+)

[a]Isolated yield after chromatography. [b]Determined by chiral GC. [c]Reaction with 1.5 mol % $[RhCl(C_2H_4)_2]_2$ and 3.3 mol % of ligand **8**. [d]Reaction for 6 days. [e]The pinacol boronate was added via syringe pump.

ligand **8** (77% and 95% ee), while ligand *ps-ent*-**8b** gave **3b** in higher stereoselectivity but in the same yield as previously (entries 4, 5).

As observed for arylboronic acids[24] and as in the case of boronate **7b**, ligands **8** and *ps-ent*-**8b** consistently yielded 1,4-adducts in opposite configuration (cf. Table 2). At 60 °C, methoxy-substituted 3-pyridinyl MIDA boronate **7c** led to a reduced yield but high enantioselectivity (entries 6, 7). Reduction of the temperature and a longer reaction time greatly improved the yield and stereoselectivity for the run with ligand **8** (80%, 95% ee) (entry 8). The experiment with *ps-ent*-**8b** at rt but for 16 h led to 98% ee but only a moderate yield (entry 9). In contrast to the racemic reactions, 3- and 4-pyridinyl MIDA boronates **7d–f** and **7h** as well as pinacol boronates **4f** and **4h** did not yield any product in the presence of **8** or *ps-ent*-**8b**. Unfortunately, neither a longer reaction time nor altered conditions led to any improvement.

All asymmetric reactions involving five-membered heteroraryl residues were conducted at rt. With 3-furanyl MIDA boronate **7i**, the reaction led to adduct **3i** in yields around 20% with >90% ee; by replacing **7i** with pinacol boronate **4i**, the yield was almost doubled while the ee was slightly lower (entries 10–12). For the challenging 2-thienyl MIDA ester **7j**, the yields were modest, while high levels of stereoinduction were retained (entries 13, 14); pinacol boronate **4j** gave very similar results (entry 15). With 2-furanyl MIDA and pinacol esters **7k** and **4k**, the yields did not exceed 20%, and for the experiments with ligand **8**, a drop in stereoselectivity was observed, while *ps-ent*-**8b** produced **3k** with 90% ee (entries 16–18). *N*-Boc 2-pyrrolyl MIDA boronate **7m** did not yield any product, but pinacol boronate **4n** with an electron-donating *N*-methyl group gave **3n** in 81% yield with 82% ee (entry 19). Finally, pinacol boronate **4o** with the *N*-TIPS 3-pyrrolyl residue yielded 56% of **3o** with 94% ee (entry 20).

The results from our studies can be interpreted as follows: Both heteroaryl MIDA and pinacol boronates are suitable for racemic 1,4-addition, but the efficiency of the reaction strongly depends on the electronic nature of the heteroaromatic system and on the position of the boronate group. In the pyridinyl series, the reaction is successful for 3- and 4-pyridinylboronates

dx.doi.org/10.1021/ol502630w | *Org. Lett.* 2014, 16, 5212–5215

and electron-donating substituents lead to improved results. In the series of five-membered heteroaryl groups, pinacol boronates tend to give higher yields than MIDA boronates and 3-pyrrolyl, thienyl, and furanyl derivatives produce the best results. For 2-boronated pyrrolyl, thienyl, and furanyl compounds, yields vary greatly with the heteroaryl group. Good to excellent results are obtained for electron-rich 2-pyrrolylboronates, while thienyl and furanyl reagents at best give moderate yields. The asymmetric reaction is even more sensitive toward the substrate. Of the pyridine series, only the methoxy-substituted 3-pyridinyl derivative gives the desired product. For five-membered heteroaryl residues, high yields are obtained with 3-thienyl and pyrrolyl derivatives, while those for 3-furanylboronates are moderate. 2-Thienyl and furanyl derivatives produce modest yields, and for 2-pyrrolylboronates, only the electron-rich substrate was successful. Further, it should be noted that all but three of the asymmetric reactions gave more than 90% ee.

The modest yields for many reactions from Table 2 may be caused by two distinctive factors: (1) Protodeboration of the heteroarylboronic acids liberated from the respective boronate may be faster than transmetalation to the rhodium catalyst or (2) after transmetalation, protoderhodation of the heteroaryl-rhodium complex may become a competing side reaction to the desired 1,4-addition. We are currently conducting NMR studies to elucidate which of these factors is crucial for 1,4-additions with heterorarylboronates. Adjusting the decomposition rate of the boronate reagent may to some extent avoid unproductive protodeboration of the liberated heteroaylboronic acid. The transmetalation and/or the carborhodation steps may become faster by employing modified catalysts, e.g. rhodium complexes of electron-deficient phosphines.[26]

In conclusion, we have presented an extensive study on heteroarylboronates in racemic and stereoselective rhodium-catalyzed 1,4-additions. Further studies, aiming to improve product yields and the scope of the asymmetric version, are currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details, characterization data, copies of spectra and chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support by the DFG (BO 1938/5-1), Rodos BioTarget GmbH, and a DFG Heisenberg Fellowship for M.M.K.B. (BO 1938/4-1) is gratefully acknowledged. The authors thank BSc. Nicola Steinke (Leibniz University of Hannover) for studies on MIDA boronate **7c** during her project work.

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