ORGANIC LETTERS

2013
Vol. 15, No. 17
4284–4287

Synthesis of *trans*-2-(Trifluoromethyl)cyclopropanes via Suzuki Reactions with an *N*-Methyliminodiacetic Acid Boronate

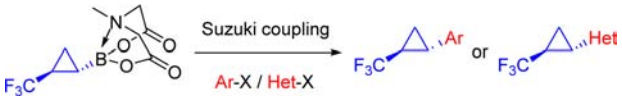
Matthew A. J. Duncton* and Rajinder Singh

Rigel, Inc., 1180 Veterans Boulevard, South San Francisco, California 94080, United States

mduncton@rigel.com; mattduncton@yahoo.com

Received June 11, 2013

ABSTRACT



***trans*-2-(Trifluoromethyl)cyclopropylboronic acid *N*-methyliminodiacetic acid (MIDA) ester 5 was synthesized as a pure diastereomer from vinylboronic acid MIDA ester and (trifluoromethyl)diazomethane in a single step. An X-ray study confirmed the *trans*-stereochemistry around the cyclopropyl ring. Use of 5 in Suzuki reactions, with a variety of aryl or heteroaryl coupling partners, provided *trans*-2-(trifluoromethyl)cyclopropyl products in moderate to excellent yields (17−90%).**

In recent years, medicinal chemists have described the advantageous use of small groups for modulating multiple properties in tandem, such as on-target potency, drug metabolism, and pharmacokinetic properties (DMPK) or toxicological (safety) profile. For instance, numerous publications have described the beneficial effects of cyclopropyl,[1] trifluomethyl,[2] oxetan-3-yl,[3] and other small motifs on the above characteristics.[4] One moiety that has been under explored in this regard, is the 2-(trifluoromethyl)-cyclopropyl group **1** (Figure 1). To date, only a small number of publications have detailed the use of 2-(trifluoromethyl)cyclopropanes within a medicinal chemistry setting. For example, a small series of potent transient receptor potential vanilloid 1 (TRPV1) antagonists containing a 2-(trifluoromethyl)cyclopropyl group have been disclosed in the patent and primary literature.[5,6] Other occurrences tend to detail single compounds as part of a broader grouping.[7] The limited use of a 2-(trifluoromethyl)-cyclopropyl fragment by medicinal chemists is unfortunate, as its incorporation combines two substructures frequently encountered in medicinal chemistry programs, the cyclopropyl and trifluoromethyl groups, in a three-dimensional, chiral framework. This three-dimensional and chiral topology may in itself be desirable, as these features have been noted to result in a positive influence on DMPK and selectivity profiles in some instances.[8,9] Interestingly, recent experiences with 1-(trifluoromethyl)cyclopropanes, close structural cousins to 2-(trifluoromethyl)cyclopropyl counterparts, demonstrate a positive effect on metabolic stability when compared with a *tert*-butyl congener.[10] Beyond the realm of medicinal chemistry, 2-(trifluoromethyl)cyclopropanes may be useful in materials science, where the unique electronic properties

(1) Salaun, J. *Topics Curr. Chem.* **2000**, *207*, 1.
(2) (a) Yale, H. L. *J. Med. Chem.* **1959**, *1*, 121. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem Soc. Rev.* **2008**, *37*, 320. (c) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950.
(3) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Muller, K. *J. Med. Chem.* **2010**, *53*, 3227.
(4) Kettle, J. G.; Ward, R. A.; Griffen, E. *Med. Chem. Commun.* **2010**, *1*, 331 and references cited therein.
(5) Kelly, M. G.; Kincaid, J.; Janagani, S.; Duncton, M. U.S. Patent 0205773, 2006; *Chem. Abstr.* **2006**, *145*, 336048.
(6) Duncton, M. A. J.; Ayala, L.; Kaub, C.; Janagani, S.; Edwards, W. T.; Orike, N.; Ramamoorthy, K.; Kincaid, J.; Kelly, M. G. *Tetrahedron Lett.* **2010**, *51*, 1009.
(7) See the Supporting Information for a full discussion.
(8) (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Lovering, F. *Med. Chem. Commun.* **2013**, *4*, 515.
(9) Clemons, P. A.; Bodycombe, N. E.; Carrinski, H. A.; Wilson, J. A.; Shamji, A. F.; Wagner, B. K.; Koehler, A. N.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 18787.
(10) Barnes-Seeman, D.; Jain, M.; Bell, L.; Ferreira, S.; Cohen, S.; Chen, X. H.; Amin, J.; Snodgrass, B.; Hatsis, P. *ACS Med. Chem. Lett.* **2013**, *4*, 514.

10.1021/ol401636d
Published on Web 08/16/2013

of fluorine and cyclopropane may offer an ability to fine-tune individual properties.

The limited use of 2-(trifluoromethyl)cyclopropanes by chemists may, in part, be due to a small number of techniques for synthesizing such compounds (Figure 1).[11] For instance, the vast majority of methods for preparing 2-(trifluoromethyl)cyclopropyl products rely on a metal-catalyzed cyclopropanation of an alkene with (trifluoromethyl)diazomethane **2**, with the diazo species generated in a step prior to cyclopropanation or in situ during the cyclopropanation process.[11−13] Uses of this approach include studies by Morandi and Carreira on ruthenium-catalyzed cyclopropanation of styrene starting materials with (trifluoromethyl)diazomethane **2**, generated in situ.[13] However, only seven examples with styrenes were detailed, and no examples with heteroaromatic substrates were reported. A complementary technique for preparing 2-(trifluoromethyl)cyclopropanes utilizes a Suzuki reaction with dibutyl 2-(trifluoromethyl)-cyclopropylboronate **3**, which is itself also derived from (trifluoromethyl)diazomethane **2**.[5,6] The disadvantage with this approach is that the boronate coupling partner **3** is a liquid, and it is used as a mixture of *cis*- and *trans*-isomers (ca. 2:3 ratio), giving rise to a mixture of geometrical isomers in the coupled products. Recently, another method for synthesizing 2-(trifluoromethyl)cyclopropanes has been reported. This approach uses a ruthenium-catalyzed Kharasch reaction of alkenes with halothane ($F_3CCHBrCl$), followed by dehalogenation/cyclization.[14] However, a large excess of halothane and magnesium reagents are required, and mixtures of *cis*- and *trans*-isomers are obtained in some cases. Again, no examples with heteroaromatic substrates were reported. Other methods for preparing 2-(trifluoromethyl)cyclopropanes have included additions to β-(trifluoromethyl)vinyl sulfonium salts with active methylene compounds.[15] However, no examples to provide 1-heteroaryl-2-(trifluoromethyl)-cyclopropanes have been disclosed.

Regardless of the limitations described above for dibutyl 2-(trifluoromethyl)cyclopropylboronate **3**, the use of a cross-coupling strategy to prepare 2-(trifluoromethyl)-cyclopropanes is an attractive concept, as the method can be applied to a diverse array of aryl and heteroaryl substrates. Additionally, (trifluoromethyl)diazomethane **2** is used only once, in the preparation of a suitable boronate coupling partner, which can then be utilized for multiple Suzuki reactions. Such a coupling strategy would be even more valuable if a suitable coupling partner could be generated in solid form and as a single geometrical isomer. In this paper, we disclose a method for preparing a wide variety of racemic *trans*-2-(trifluoromethyl)cyclopropane products by synthesizing *trans*-2-(trifluoromethyl)-cyclopropylboronic acid MIDA ester, which functions as a readily handled and air-stable, solid donor of a *trans*-2-(trifluoromethyl)cyclopropyl group in Suzuki reactions.[16,17] In particular, we have focused on introducing the *trans*-2-(trifluoromethyl)cyclopropyl group into templates frequently encountered within drug discovery laboratories, such as functionalized aromatics or heteroaromatic rings.

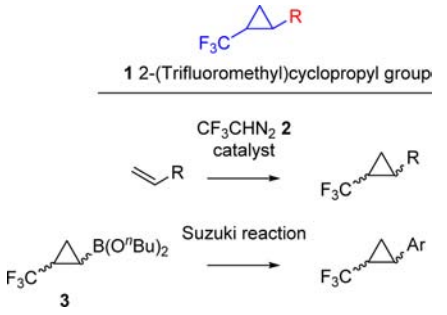


Figure 1. Synthesis of 2-(trifluoromethyl)cyclopropanes.

Our synthesis of *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester **5** began by examining the addition of (trifluoromethyl)diazomethane **2** to vinylboronic acid MIDA ester **4**[18] under palladium-catalysis.[5,6] Gratifyingly, this reaction proceeded uneventfully to give a 61−87% yield of the cyclopropanated product after column chromatography on silica gel (Scheme 1). To our delight, the reaction provided only the *trans*-isomer as a free-flowing solid. The *trans*-stereochemistry was confirmed from an X-ray crystallographic study after recrystallization from 1,2-dichloroethane. In contrast, a similar cyclopropanation reaction undertaken with vinylboronic acid dibutyl ester provided dibutyl 2-(trifluoromethyl-)cyclopropylboronate **3** as a liquid and a 2:3 mixture of *cis*- and *trans*-isomers.[5,6] The increase in stereoselectivity observed for cyclopropanation of **4** may be attributed to reaction of a bulky and conformationally rigid MIDA ester, promoting reaction from only one face of the alkene.[19] Importantly, the cyclopropanation reaction to provide MIDA boronate **5** could be undertaken on a multigram scale without any reduction in yield or stereochemical integrity of the product. Similar to other MIDA esters,[18−21] compound **5** requires no special handling and is stable to

(11) For a review on the synthesis of (trifluoromethyl)cyclopropanes, see: Grygorenko, O. O.; Artamonov, O. S.; Komarov, I. V.; Mykhailiuk, P. K. *Tetrahedron* **2011**, *67*, 803.

(12) (a) Le Maux, P.; Juillard, S.; Simonneaux, G. *Synthesis* **2006**, 1701. (b) Mykhailiuk, P. K.; Afonin, S.; Ulrich, A. S.; Komarov, I. V. *Synthesis* **2008**, 1757.

(13) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938.

(14) Risse, J.; Fernández-Zúmel, M. A.; Cudré, Y.; Severin, K. *Org. Lett.* **2012**, *14*, 3060.

(15) (a) Lin, H.; Shen, Q.; Lu, L. *J. Org. Chem.* **2011**, *76*, 7359. (b) Kasai, N.; Maeda, R.; Furuno, H.; Hanamoto, T. *Synthesis* **2012**, *44*, 3489.

(16) Duncton, M.; Singh, R. Patent WO 075316, 2012; *Chem. Abstr.* **2012**, *157*, 76933.

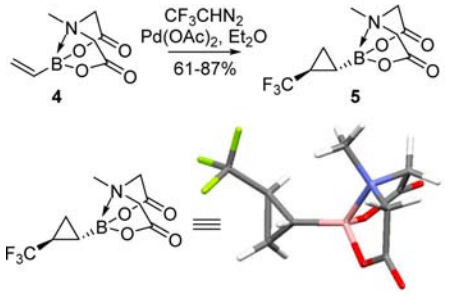
(17) For a review on the benefits of boronic acid MIDA esters, see: Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* **2009**, *42*, 17.

(18) (a) Uno, B. C.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130. (b) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716.

(19) (a) Mancilla, T.; Contreras, R.; Wrackmeyer, B. *J. Organomet. Chem.* **1986**, *307*, 1. (b) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084.

prolonged storage under benchtop conditions (ambient temperature and air). Thus, the results above also provide another illustration as to the advantages of MIDA boronate chemistry, when compared to experiences with alternative boronic esters or the parent boronic acid. Importantly, the synthesis of compound **5** adds another valuable building block to the MIDA family of reagents, which are rapidly emerging as a versatile toolbox of stable boronic acid surrogates, for drug discovery and natural product synthesis.[20,21]

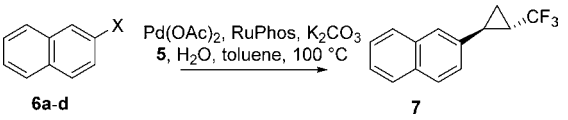
Scheme 1. Synthesis and X-ray Structure of **5**[a]



[a] Crystal image simplified for clarity (see the Supporting Information).

Next, we examined the use of (trifluoromethyl)cyclopropyl MIDA boronate **5** in palladium(0)-catalyzed Suzuki reactions (Tables 1 and 2).[22] It was found that **5** could readily participate in such cross-couplings.[23] For example, Suzuki reactions could be undertaken with aryl iodide, triflate, bromide, or chloride starting materials, using a model naphthyl example (Table 1). As expected, the yield of the *trans*-2-(trifluoromethyl)cyclopropyl coupled product **7** was greatest when starting from an aryl iodide or aryl triflate (both giving a 78% yield; entries 1 and 2), as opposed to starting from an aryl bromide or aryl chloride (65% and 54% yield respectively; entries 3 and 4). Further reactions, predominately using bromo-containing starting materials due to their commercial availability, demonstrate that a multitude of functional groups commonly encountered in medicinal or synthetic organic chemistry were tolerated in the coupling partners (Table 2). For instance, compounds containing fluoro, nitro, anilino, tetrazolone, alkyl, ketone, pentafluorosulfur, ether, ester, acetal, and lactam groups were not affected under the reaction conditions, giving rise to the expected *trans*-2-(trifluoromethyl)cyclopropyl coupled products in moderate to excellent yields (entries 1–15). Of special note were Suzuki reactions with a wide variety of heteroaromatic coupling partners (entries 9–15). These were particularly significant since a large percentage of marketed drugs contain a heterocyclic core.[24] Thus, Suzuki reactions with MIDA boronate **5** may present a particularly useful method for introducing a *trans*-(trifluoromethyl)cyclopropyl group into a heterocyclic substrate. This is noteworthy since previous studies to prepare (trifluoromethyl)cycloropyl products, using a 2 + 1 cycloaddition between an alkene and (trifluoromethyl)diazomethane, have detailed few examples employing a heterocyclic starting material.[11–13]

Table 1. Coupling with Halides or Pseudohalides



entry	X	yield of **7** (%)
1	I (**6a**)	78
2	OTf (**6b**)	78
3	Br (**6c**)	65
4	Cl (**6d**)	54

Taken together, the results presented above provide a broad illustration of the utility of MIDA boronate **5** in Suzuki cross-couplings. Presumably, these reactions occur in a similar fashion to couplings with other MIDA boronates, via in situ release of the corresponding boronic acid from the MIDA ester starting material under the basic conditions encountered in the reaction media.[25] Significantly, many of the 2-(trifluoromethyl)cyclopropyl products described above are relatively low in molecular weight and are compliant with "rule-of-three" criteria[26] describing attractive fragments for medicinal chemists.[27]

In summary, this paper describes the synthesis of *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester **5** and its use in Suzuki cross-coupling reactions with aryl or heteroaryl substrates. By virtue of its unique structure and three-dimensional chiral framework, the introduction of a *trans*-2-(trifluoromethyl)cyclopropyl group may present a particularly useful fragment for chemists engaged in drug discovery or materials science. Furthermore, our studies provide another illustration as to the benefits of MIDA boronate chemistry for solving a challenging synthetic

(20) For select examples of MIDA boronates in natural products synthesis, see: (a) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466. (b) Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 6941. (c) Lee, S. J.; Anderson, T. M.; Burke, M. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8860. (d) Brak, K.; Ellman, J. A. *Org. Lett.* **2010**, *12*, 2004. (e) Fujii, S.; Chang, S. Y.; Burke, M. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 7862. (f) Gray, K. C.; Palacios, D. S.; Dailey, I.; Endo, M. M.; Uno, B. E.; Wilcock, B. C.; Burke, M. D. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 2234.

(21) Grob, J. E.; Nunez, J.; Dechantsreiter, M. A.; Hamann, L. G. *J. Org. Chem.* **2011**, *76*, 10241.

(22) (a) Wallace, D. J.; Chen, C. *Tetrahedron Lett.* **2002**, *43*, 6987. (b) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

(23) For a review, see: Gagnon, A.; Duplessis, M.; Fader, L. *Org. Prep. Proced. Int.* **2010**, *42*, 1 and references cited therein.

(24) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887.

(25) (a) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961. (b) Lennox, A. J. J.; Lloyd-Jones, G. C. *Israel J. Chem.* **2010**, *50*, 664.

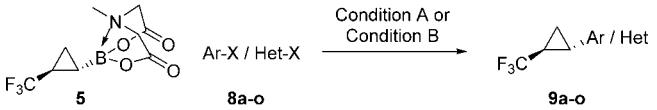
(26) Congreve, M.; Carr, R.; Murray, C.; Jhoti, H. *Drug Discovery Today* **2003**, *8*, 876.

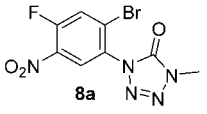
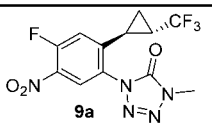
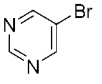
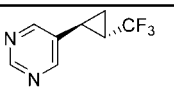
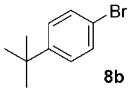
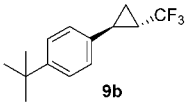
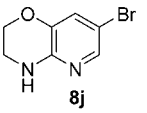
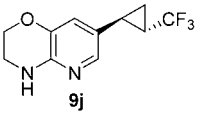
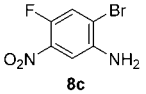
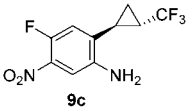
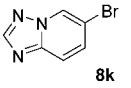
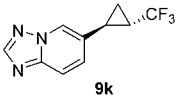
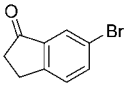
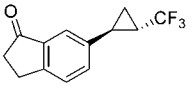
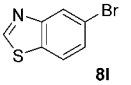
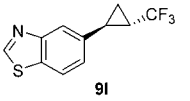
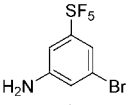
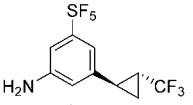
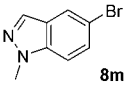
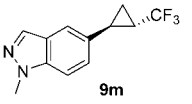
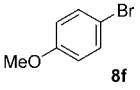
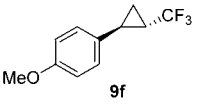
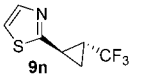
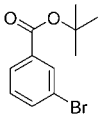
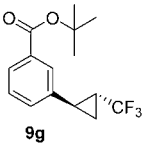
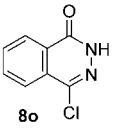
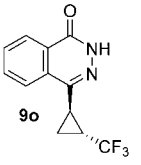
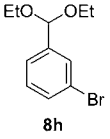
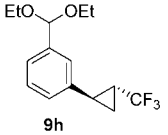
(27) See the Supporting Information for full details.

(28) For asymmetric syntheses of 2-(trifluoromethyl)cyclopropanes, see ref 12a and Morandi, B.; Mariampillai, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1101.

(29) We have undertaken a chiral synthesis of a *trans*-2-(trifluoromethyl)cyclopropylboronic acid equivalent. Results will be reported in due course.

Table 2. Suzuki Couplings with Boronate Ester **5**[*]



entry	Ar-X or Het-X	product	yield (%)	entry	Ar-X or Het-X	product	yield (%)
1	 **8a**	 **9a**	67[a]	9	 **8i**	 **9i**	32[f]
2	 **8b**	 **9b**	81[b]	10	 **8j**	 **9j**	17[g]
3	 **8c**	 **9c**	54[c]	11	 **8k**	 **9k**	56[d]
4	 **8d**	 **9d**	90[b]	12	 **8l**	 **9l**	72[d]
5	 **8e**	 **9e**	76[d]	13	 **8m**	 **9m**	33[d]
6	 **8f**	 **9f**	24[b] / 58[b]	14	 **8n**	 **9n**	33[d]
7	 **8g**	 **9g**	23[b] / 44[e]	15	 **8o**	 **9o**	31[d]
8	 **8h**	 **9h**	69[b]				

[*] Conditions A: $Pd(OAc)_2$, Cy_3P, Cs_2CO_3 or K_2CO_3, toluene, H_2O, heat. Conditions B: Pd(OAc), RuPhos, K_2CO_3, toluene, H_2O, heat. [a] Conditions A with Cs_2CO_3 at 80 °C. [b] Conditions B at 100 °C. [c] Conditions A with Cs_2CO_3 at reflux. [d] Conditions B at 115 °C. [e] Conditions B at 80 °C. [f] Conditions A with K_2CO_3 at reflux. [g] Conditions A with K_2CO_3 at 115 °C (see the Supporting Information for individual reaction conditions).

problem. Future work will focus on a homochiral synthesis of *trans*-2-(trifluoromethyl)cyclopropyl products[28,29] and a further examination of the medicinal chemistry qualities associated with the *trans*-2-(trifluoromethyl)cyclopropyl group.

Acknowledgment. We thank Dr. Peter S. White (University of North Carolina at Chapel Hill) for performing the X-ray analysis with compound **5**. We also thank Prof. Martin D. Burke (University of Illinois at Urbana–Champaign) for insightful discussions regarding the synthesis and use of MIDA boronates and Mark Irving, Van Ybarra, and Duayne Tokushige of Rigel, Inc. analytical chemistry for high-resolution mass spectrometry.

Supporting Information Available. Details of known 2-(trifluoromethyl)cyclopropanes. Discussion of log *P* for 2-(trifluoromethyl)cyclopropanes, experimental details, and analytical data for compounds **5**, **7**, and **9a**–**o**. X-ray data for compound **5** (CIF; see also CCDC 955803). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare the following competing financial interest(s): The authors are employees of Rigel, Inc. and receive compensation, including stock-based awards.