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Metal-Catalyzed Release of Supported Boronic Acids for C–C Bond Formation

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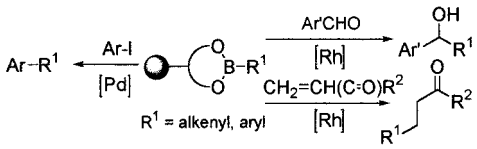
ABSTRACT



The viability of solid-supported boronic acids as reagents for Suzuki couplings and nucleophilic additions to aldehydes and enones was successfully demonstrated. This metal-catalyzed cleavage strategy allows the synthesis of a series of functionalized biphenyl products, benzylic alcohols, and *β*-substituted ketones.

Solid-phase reactions play an important role in parallel synthesis and combinatorial chemistry, particularly in the area of medicinal chemistry, where their potential has emerged as a result of the possibility of automation.[1] A considerable amount of attention has been focused on adapting and exploiting the advantages of solid-phase synthesis (SPS) for the production of libraries of nonoligomeric, small organic molecules for biological screening.[2] In this context, transition-metal-promoted reactions serve as efficient methods because they proceed under mild conditions and are compatible with many functional groups.[3] For instance, solid-phase Suzuki coupling has been largely developed mainly by reacting a resin-bound aryl halide with a solution-phase boronic acid.[4−5] However, this strategy suffers from the fact that there is a limited number of commercially available aryl boronic acids.[6] We recently reported the preparation of a macroporous support (**1**) that can be employed to efficiently immobilize and transform functionalized arylboronic acids.[7,8] One of the major advantages of this boronate linker system is its possible use in a resin capture process.[9] Since the biaryl subunit is an important pharmacophore, present in a variety of biologi-

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(1) (a) *Molecular Diversity and Combinatorial Chemistry*; Chaiken, I. M., Janda, K. D., Eds; American Chemical Society: Washington, DC, 1996. (b) *Combinatorial Chemistry*; Wilson, S. R., Czarnik, A. W., Eds; Wiley-Interscience: New York, 1997.

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(3) (a) Kingsbury, C. L.; Mehrman, S. J.; Takacs, J. M. *Curr. Opin. Chem.* **1999**, *3*, 497−555. (b) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549−1581. (c) Wendeborn, S.; De Mesmaeker, A.; Brill, W. K.-D.; Berteina, S. *Acc. Chem. Res.* **2000**, *33*, 215−224.

(4) Original references of solid-phase Suzuki reactions: (a) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177−9180. (b) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171−11172.

(5) For a selection of recent examples of solid-phase Suzuki reactions, see: (a) Huwe, C. M.; Künzer, H. *Tetrahedron Lett.* **1999**, *40*, 683−686. (b) Blettner, C. G.; König, W. A.; Rhüter, G.; Stenzel, W.; Schotten, T. *Synlett* **1999**, 307−310. (c) Chamoin, S.; Houldsworth, S.; Kruse, C. G.; Iwema Baker, W.; Snieckus, V. *Tetrahedon Lett.* **1998**, *39*, 4179−4182. (d) Amparo Lago, M.; Nguyen, T. T.; Bhatnagar, P. *Tetrahedron Lett.* **1998**, *39*, 3885−3888. (e) Wendeborn, S.; Berteina, S.; Brill, W. K.-D., De Mesmaeker, A. *Synlett* **1998**, 671−675. (f) Lorsbach, B. A.; Bagdanoff, J. T.; Bryan Miller, R.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 2244−2250. (g) Garigipati, R. S. *Tetrahedron Lett.* **1997**, *38*, 6807−6810. (h) Yoo, S.-E.; Seo, J.-S.; Yi, K.-Y.; Gong, Y.-D. *Tetrahedron Lett.* **1997**, *38*, 1203−1206. (i) Brown, S. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 7076−7077. (j) Ruhland, B.; Bombrun, A.; Gallop, M. A. *J. Org. Chem.* **1997**, *62*, 7820−7826. (k) Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169−5171. (l) Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219−8222.

(6) In comparison to more than 1500 commercially available carboxylic acids, only 100−150 different boronic acids are offered by Aldrich and Lancaster.

(7) Carboni, B.; Pourbaix, C.; Carreaux, F.; Deleuze, H.; Maillard, B. *Tetrahedron Lett.* **1999**, *40*, 7979−7983.

(8) For other preparations of resin-bound boronic acids, see: Hall, D. G.; Taylor, J.; Gravel, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3064−3067.

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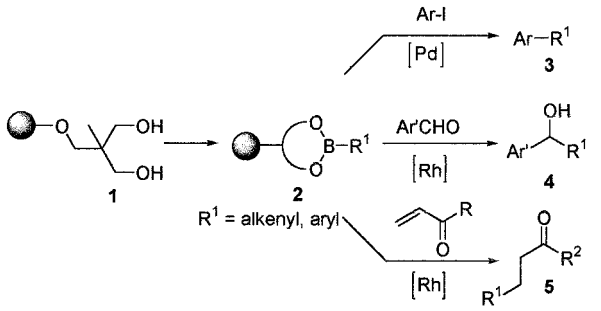
cally active compounds,[10] we wished to determine whether the synthesis of this structure could be carried out from supported arylboronic acids.

To the best of our knowledge, only one linear-solid-phase strategy was so far reported based on immobilization of boronic acids, which enables the concomitant formation of a carbon−carbon bond and the functionalization within the cleavage step.[11,12] In this traceless approach, attachments of boronic acids were indirectly achieved in a multistep procedure and with the help of an auxiliary amide-containing spacer.

We describe herein the successful use of supported boronic acids **2** as reagents not only in the Suzuki cross-coupling reactions but also in addition reactions to aldehydes and enones by metal-catalyzed cleavage procedures (Scheme 1).

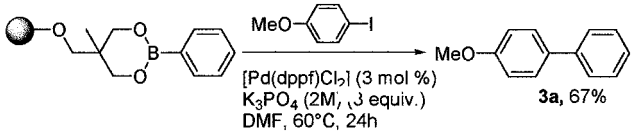
Scheme 1



With the lack of an auxiliary spacer, our strategy offers the additional advantage of attachment of boronic acids in a single step by direct loading.

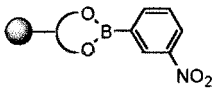
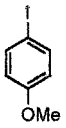
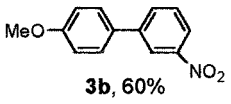
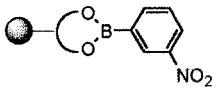
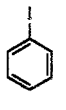
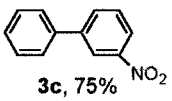
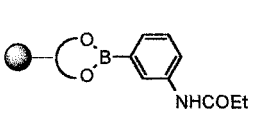
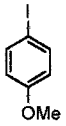
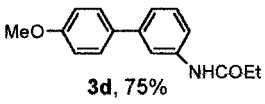
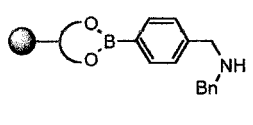
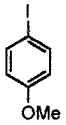
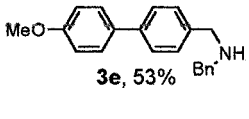
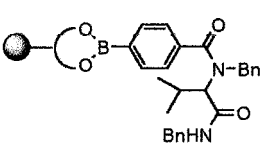
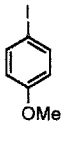
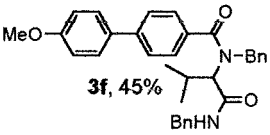
To find an efficient procedure for the Suzuki coupling of supported arylboronic acids **2**, preliminary experiments have been performed on a model system. The resin-bound phenylboronic acid was treated with 4-iodomethoxybenzene under standard palladium coupling conditions.[13] Analysis of the resulting crude mixtures showed the presence of two compounds: the desired product along with biphenyl derived from homocoupling of the organoborane.[14] Several combinations of catalyst and base were tested to optimize the yield and to lower the formation of the side product. The best result was obtained with [Pd(dppf)Cl_2] in association with K_3PO_4 (dppf = 1,1′-bis(diphenylphosphanyl)ferrocene). By using this catalytic system and 5 equiv of 4-iodomethoxybenzene, the yield of the desired biaryl product was 67%, the crude product still being contaminated by 5% of the homocoupling product (Scheme 2).[15]

Scheme 2



This cleavage was further examined with different aryl ring systems, and the liberated products were isolated in moderate to good yields (Table 1). As significant demonstration of the potential of this cleavage strategy and the usefulness of resin **1** to generate new aryl boronic acids, the coupling reaction was realized with a functionalized resin-bound boronic acid, which was obtained from an UGI four-component condensation (entry 5).[9] ^{1}H NMR of the crude material isolated from the resin indicated the formation of only the desired product **3f** (no homocoupling) along with the excess of the 4-iodomethoxybenzene.

Table 1. Suzuki Coupling−Release of Various Functionalized Resins

Entry	Resin	Aryl iodide	Product Yield (%)[a]
1			 **3b**, 60%
2			 **3c**, 75%
3			 **3d**, 75%
4			 **3e**, 53%
5			 **3f**, 45%

[a] Yields of isolated products based on the loading of the resin **1** (1 mmol/g). All compounds were purified by flash chromatography on silica gel.

(9) (a) McCarthy, P. A. *Med. Res. Rev.* **1993**, *13*, 139−159. (b) Pavia, M. R.; Cohen, M. P.; Dilley, G. J.; Dubuc, G. R.; Durgin, T. L.; Forman, F. W.; Hediger, M. E.; Milot, G.; Powers, T. S.; Sucholeiki, I.; Zhou, S.; Hangauer, D. G. *Bioorg. Med. Chem.* **1996**, *4*, 659−666.

(10) Pourbaix, C.; Carreaux, F.; Carboni, B.; Deleuze, H. *Chem. Commun.* **2000**, 1275−1276.

(11) Li, W.; Burgess, K. *Tetrahedron Lett.* **1999**, *40*, 6527−6530.

(12) Recently, a successful strategy for resin-to-resin Suzuki coupling reactions via phase transfer of solid-supported arylboronic acids was described: Gravel, M.; Bérubé, C. D.; Hall, D. G. *J. Comb. Chem.* **2000**, *2*, 228−231.

(13) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

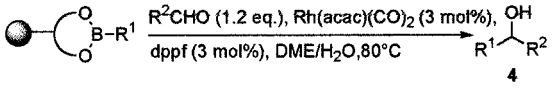
(14) Yamaguchi, S.; Ohno, S.; Tamao, K. *Synlett* **1997**, 1199−1201.

(15) The yield was measured by GC versus benzophenone internal standard relative to the loading of resin **1** (1 mmol/g). The mixture was passed through silica plugs to remove excess ligand/metal before analysis.

Recently, it was demonstrated that the transmetalation between boron and rhodium provided another C−C bond-forming reaction via the 1,2-addition of aryl or 1-alkenylboronic acids to aldehydes[16] and the 1,4-addition to α,β-unsaturated ketones.[17] A catalytic asymmetric 1,4-addition to enones has been reported by Hayashi and co-workers.[17b,c] The efficiency of the protocol was also demonstrated in similar addition reactions of organotrifluoroborate salts.[18] We envisioned that supported boronic acids also could be good reagents for the aforementioned Rh(I)-catalyzed reactions. To the best of our knowledge, no examples of successful application of these reactions on solid phase have been described so far. Of particular interest is that, in contrast to biphenyl, the structures obtained in these reactions are more rarely found in pharmaceutical compounds, which makes this process attractive for the preparation of original libraries.

For initial studies, we opted to adapt the conditions developed by Miyaura and co-workers for the arylation of aldehydes.[16a] Reaction of resin-bound *p*-methylphenylboronic acid with 1 equiv of benzaldehyde, $Rh(acac)(CO)_2$ (3 mol %), and the ligand dppf (3 mol %) resulted in the formation of the desired benzyl alcohol **4a**. The unreacted aldehyde was easily removed using the diol resin **1** as solid-support scavenger of aldehydes.[19] After cleavage, the crude product was combined with polymer **1** at reflux in THF in the presence of PTSA (cat.) to afford **4a** in 62% yield and with a high purity (>95%) (Table 2, entry 1). The increase of the amount of benzaldehyde to 2 equiv resulted in a significant drop in the product yield to 44%. A variety of aldehydes were functionalized in this manner to give the corresponding benzylic alcohols **4** in moderate to good yields but with a good purity (>95%) in all cases (entries 2−5).

Table 2. Arylation of Aldehydes with Supported Boronic Acids



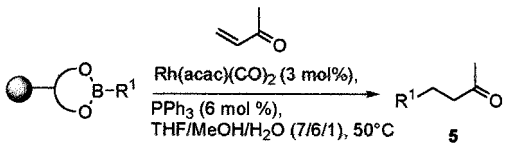
4

entry	R^1	R^2	alcohol	yield (%)[a]	purity (%)[b]
1	4-MeC_6H_4	Ph	**4a**	62	>95
2	4-MeC_6H_4	4-ClC_6H_4	**4b**	43	>95
3	4-MeC_6H_4	$4\text{-F}_3\text{CC}_6H_4$	**4c**	63	>95
4	4-MeC_6H_4	4-NCC_6H_4	**4d**	81	>95
5	Ph	4-NCC_6H_4	**4e**	56	>95

[a] Yields of isolated products based on the loading of the resin **1** (1 mmol/g). [b] GC purity of the crude reaction mixture. The mixture was passed through silica plugs to remove excess ligand/metal before analysis.

The supported boronic acids **2** were also useful reagents for nucleophilic 1,4-additions to enones. Methyl vinyl ketone (MVK) was chosen as representative substrate.[20] By using 1.2 equiv of resin-bound phenylboronic acid in the presence of $Rh(acac)(CO)_2$ (3 mol %) and triphenylphoshine (6 mol %), the β-functionalized ketone **5a** was obtained in 50% yield (Table 3, entry 1). The use of a large excess of MVK (5 equiv) noticeably improved the isolated yield to 60% (entry 2). The supported 1-hexenylboronic acid also reacted with MVK using the same protocol, giving a comparable isolated yield of the product **5c** (entry 4). In each case, the material liberated from the resin was relatively pure (>95%) contaminated only with triphenylphosphine oxide.

Table 3. Conjuguate Arylation and Alkenylation of MVK with Supported Boronic Acids



5

entry	R^1	MVK (equiv)	ketone	yield (%)[a]	purity (%)[b]
1	Ph	1.2	**5a**	50	>95
2	Ph	5	**5a**	60	>95
3	4-MeC_6H_4	5	**5b**	47	>95
4	1-hexenyl	5	**5c**	55	>95

[a] Yields of isolated products based on the loading of the resin **1** (1 mmol/g). All compounds were purified by flash chromatography on silica gel. [b] Determined by ^1H NMR (apart from triphenylphosphine oxide).

In conclusion, we successfully demonstrated the viability of supported boronic acids as reagents for Suzuki couplings and nucleophilic additions to aldehydes and enones. This metal-catalyzed cleavage strategy allows the synthesis of a series of funtionalized biphenyl compounds, benzylic alcohols, and β-substituted ketones. Added to the potential of the resin **1** to generate libraries of several new aryl boronics acids as reagents, this strategy is particularly promising toward high-throughput combinatorial library synthesis. We are currently looking to expand this approach to other types of reactions involving boronic acids.[21]

Acknowledgment. This research was supported by the CNRS. We thank Dr. H. Deleuze (Université de Bordeaux 1) for the preparation of the diol resin **1**.

Supporting Information Available: Experimental procedures and characterizations for compounds **3b**−**f**, **4a**−**e**, and **5a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL000338Y

(16) (a) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279−3281. (b) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450−4452.

(17) (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229−4231. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479−8482. (c) Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579−5580.

(18) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683−1686.

(19) Immobilization of aldehydes using the diol resin of Leznoff was reported. Chamoin, S.; Houldsworth, S.; Kruse, C. G.; Iwema Baker, W.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4179−4182.

(20) MVK was selected because of its low boiling point.

(21) For examples, see: (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933−2936. (b) Evans, D. A.; Katz, J. L.; West, T. H. *Tetrahedron Lett.* **1998**, *39*, 2937−2940.