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Convergent, Regiospecific Synthesis of Quinolines from *o*-Aminophenylboronates

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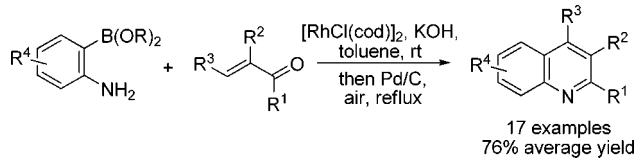
ABSTRACT



A direct convergent two-component synthesis of quinolines from α,β-unsaturated ketones and *o*-aminophenylboronic acid derivatives is reported. The reaction is regiocomplementary to the traditional Skraup−Doebner−Von Miller synthesis and proceeds under basic rather than strongly acidic conditions. Quinolines substituted in the benzenoid ring can be accessed by using substituted *o*-aminophenylboronates prepared by direct palladium-catalyzed borylation of the corresponding *o*-bromoanilines.

The quinoline ring system is an important target in synthetic chemistry. It is found in a large number of natural products, many of which have important biological activities (e.g., quinine, camptothecin).[1] Quinolines are integral to a large number of synthetic drug substances with activities including antimalarial, antiinflammatory, antineoplastic, antifungal, antiseptic/antiinfective, and analgesic properties.[2] They also find application in agrochemicals and effect chemicals such as dyestuffs and corrosion inhibitors.[3] The development of new methods for their synthesis is therefore an area of considerable ongoing interest.[4]

As part of a new program in diversity-oriented array synthesis, we have been investigating the behavior of ortho-substituted phenylboronic acids as nucleophiles in rhodium-catalyzed conjugate addition chemistry[5] and turned our attention to the commercially available 2-aminophenylboronic acid (**1**). Thus, the reaction of **1** with non-3-en-2-one was carried out under standard conditions for such conjugate additions, using the known highly active catalyst $[RhCl(cod)]_2$ and a 2-fold excess of **1** to compensate for competing protodeboronation pathways.[6] Following column

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(5) (a) Sakai, M.; Hayashi, M.; Miyaura, N. *Organometallics* **1997**, *16*, 4229–4231. (b) Yoshida, K.; Hayashi, T. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 171−203.

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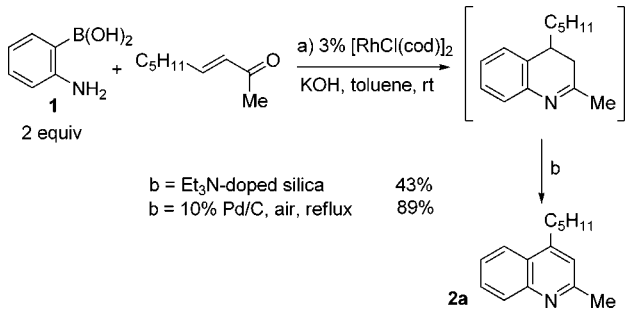
chromatography of the reaction mixture on triethylamine-doped silica gel, we isolated the quinoline **2a** in 43% yield (Scheme 1). Analysis of the crude reaction mixture by ^{1}H

Scheme 1. Novel Synthesis of Quinolines from Aminobenzene Boronic Acid



NMR shows the presence of the expected intermediate 3,4-dihydroquinoline, together with approximately equimolar amounts of **2a** and the corresponding tetrahydroquinoline, suggesting that the dihydroquinoline undergoes disproportionation under basic conditions. We recognized that this might be a useful new approach to the synthesis of substituted quinolines from enones, provided that an effective method for the oxidation of the dihydroquinoline could be found. In the event, simple addition of palladium on charcoal to the reaction vessel upon completion of the conjugate addition and heating at reflux open to air gave **2a** in a gratifying 89% yield.

The regiochemistry of the product was assigned unambiguously by NOE studies, confirming that the reaction likely proceeds by an initial rhodium-catalyzed conjugate addition of the boronic acid to the enone, followed by intramolecular condensation of the amine and ketone carbonyl.[7,8] The regiochemical outcome of the transformation is therefore complementary to the classical Skraup−Doebner−Von Miller reaction,[9] wherein the product observed in the reaction between anilines and enones is that of a formal addition of nitrogen to the β-carbon of the α,β-unsatured ketone (Figure 1).[10,11] Thus, a single enone precursor can now give rise to either isomeric quinoline by choice of the appropriate

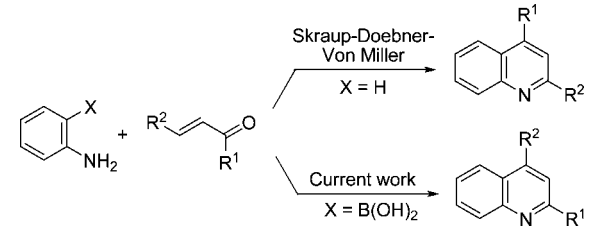
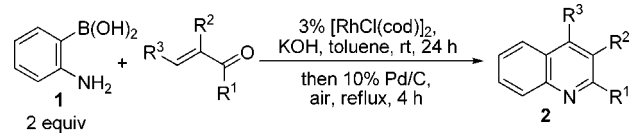


Figure 1. Comparison of quinoline synthesis by classical Skraup−Doebner−von Miller reaction and the current method.

condensation conditions. An additional complementarity is evident from the contrasting reaction conditions: the Skraup reaction typically occurs under strongly acidic conditions,[9] whereas the current method utilizes basic reagents. We therefore set out to investigate the generality of this useful new one-pot synthesis of quinolines.

We first investigated the generality and scope of the reaction with respect to the Michael acceptor component (Table 1).[12] Pleasingly, the reaction appears to have broad

Table 1. Scope of the Quinoline Synthesis: Michael Acceptor



entry	product	R^1	R^2	R^3	yield[a] (%)
1	**2a**	Me	H	C_5H_{11}	89
2	**2b**	Me	H	4-$MeOC_6H_4$	77
3	**2c**	Ph	H	Ph	96
4	**2d**	Ph	H	C_9H_{19}	62
5	**2e**	Ph	H	2-$MeOC_6H_4$	71[b]
6	**2f**	4-$MeOC_6H_4$	H	4-MeC_6H_4	79
7	**2g**	1-naphthyl	H	4-ClC_6H_4	85
8	**2h**	3-thienyl	H	4-ClC_6H_4	89
9	**2i**	2-(*N*-Me)pyrrolyl	H	4-$NO_2C_6H_4$	86
10	**2j**	2-pyridyl	H	4-$NO_2C_6H_4$	0
11	**2k**	Ph	Me	H	69[b]
12	**2l**	Ph	H	H	42[c]

[a] Isolated yield based on enone. [b] First step at 55 °C. [c] Reaction carried out at four times dilution.

applicability, with enones bearing 1,3-dialkyl, 1,3-diaryl and both regioisomeric arrangements of 1,3-alkylaryl substitution being tolerated (entries 1−4). The reaction also tolerates a wide range of aromatic substituents (electron-rich, electron-poor, and heteroaromatic), while potentially sensitive functional groups (chloro- and nitroarenes) are also unaffected

(7) The formation of heterocycles by Suzuki coupling/in situ condensation of **1** or its pinacol ester is known. For quinolone synthesis from 5-haloaryl-4-carboxylates, see: Hodgetts, K. J.; Kershaw, M. T *Org. Lett.* **2003**, *5*, 2911–2914. For 6-aminophenanthridine synthesis from *o*-haloarylnitriles, see: Gug, F.; Blondel, M.; Desban, N.; Bouaziz, S.; Vierfond, J.-M.; Galons, H. *Tetrahedron Lett.* **2005**, *46*, 3725–3727.

(8) For one-pot formation of phenanthridines from amino-protected versions of **1** by Suzuki coupling/in situ deprotection/condensation, see: (a) Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5463–5466. (b) Cochennec, C.; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 979–984. (c) Chamoin, S.; Houldsworth, S.; Kruse, C. G.; Bakker, W. I.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4179–4182.

(9) (a) Skraup, Z. H. *Monatsh. Chem.* **1880**, *1*, 316–318. (b) Doebner, O.; Von Miller, W. *Ber. Dtsh. Chem. Ges.* **1881**, *14*, 2812–2817. (c) Manske, R. H. F.; Kulka, M. *Org. React.* **1953**, *7*, 59–98. (d) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 5, pp 167−243.

(10) The mechanism of the Skraup−Doebner−Von Miller reaction is nontrivial. For a recent study, see: Denmark, S. E.; Venkataraman, S. *J. Org. Chem.* **2006**, *71*, 1668–1676.

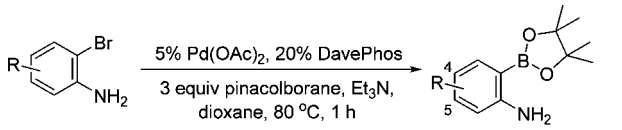
(11) For a recent example of a reversed regiochemical outcome with activated unsaturated α-ketoesters, see: Wu, Y.-C.; Liu, L.; Li, H.-J.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2006**, *71*, 6592–6595.

by the reaction conditions (entries 5−9). Alternative substitution patterns in the Michael acceptor are also tolerated, leading to 2,3-disubstituted and 2-monosubstituted products (entries 11 and 12). In the latter case, the yield of the simple natural product 2-phenylquinoline appears to be compromised by competing polymerization of the reactive Michael acceptor 1-phenylprop-2-enone, as suggested from LC−MS studies of the crude reaction mixture; optimal yields were obtained when the reaction was run under conditions of 4-fold dilution.

Interestingly, the reaction failed when an enone containing the 2-pyridyl function was used (entry 10). We presume that this is due to catalyst inhibition by coordination of the substrate, a notion supported by the unique observation of free cyclooctadiene in the crude ^{1}H NMR of this experiment. The reaction was also unsuccessful with 1,2,3-trisubstituted enones (acetylcyclohexene, 3-methylpent-3-en-2-one) and enones bearing branched 3-alkyl substituents (5-methylhex-3-en-2-one). In these cases, no Michael addition was observed, protodeboronation of **1** being the only observable process. The use of enals was also unsuccessful, with cinnamaldehyde reacting only slowly with **1** and when doing so giving rise preferentially to the 1,2-addition product.

We recognized that the value of the method would be greatly improved if it could encompass the synthesis of quinolines substituted in the benzenoid ring as well as the pyridyl ring. To this end, we required a synthesis of substituted aminophenylboronate derivatives. Guérrite has reported the direct synthesis of 2-aminophenylpinacolboronate by the palladium-catalyzed borylation of *o*-bromoaniline with pinacolborane.[13] Adaptation of this reaction to substituted bromoanilines (under slightly modified conditions) gave convenient access to the desired substituted boronates (Scheme 2). Although the yields were moderate,

Scheme 2. Palladium-Catalyzed Synthesis of Substituted 2-Aminobenzeneboronate Esters

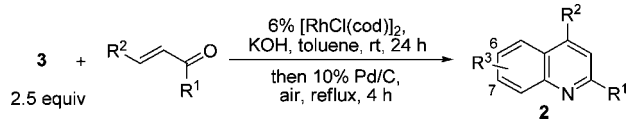


3a R = H Yield 40%
3b R = 5-Me Yield 66%
3c R = 5-^{i}Pr Yield 61%
3d R = 4-CF_3 Yield 33%

being compromised by competing hydrodebromination (the dominant reaction in the synthesis of **3d**), this one-step method uses widely available starting materials and does not require protection of the amino function.

At this stage, while we considered converting the pinacolboronate to the boronic acid, we elected instead to investigate the direct use of the pinacolboronates in the quinoline synthesis. The reactions were found to be somewhat slower than those with the boronic acid, but after some optimization, we found that the condensation of 2-aminophenylpinacolboronate (**3a**) with chalcone worked as efficiently as the corresponding boronic acid in the same time frame provided that an increased loading of both rhodium catalyst (from 3% to 6%) and base (2.0−2.5 equiv) were utilized (93% yield, cf. 96% yield from the boronic acid). The synthesis of 6- and 7-substituted quinolines was then carried out under these modified reaction conditions (Table 2). Again, the reaction proceeds smoothly, with good yields

Table 2. Synthesis of Substituted Quinolines from Aminobenzenepincacolboronates



entry	**3**	product	R^1	R^2	R^3	yield[a] (%)
1	**3a**	**2c**	Ph	Ph	H	93
2	**3b**	**2m**	Ph	Ph	6-Me	85
3	**3b**	**2n**	2-(*N*-Me)pyrrolyl	4-$NO_2C_6H_4$	6-Me	78
4	**3c**	**2o**	3-thienyl	4-ClC_6H_4	6-^{i}Pr	82
5	**3d**	**2p**	Ph	Ph	7-CF_3	81
6	**3d**	**2q**	3-thienyl	4-ClC_6H_4	7-CF_3	51
7	**3d**	**2r**	Me	C_5H_{11}	7-CF_3	68

[a] Isolated yield based upon enone.

of products being obtained with aryl- and alkyl-substituted enones. It should be noted that, in the case of the 7-substituted quinolines such as those derived from **3d**, the classical Skraup synthesis frequently gives rise to regioisomeric mixtures containing the unwanted 5-substituted isomer[6] through regioisomeric aromatic substitution pathways. The current method is regiospecific, providing another advantage over the classical approach.

In summary, we have developed a novel, regiospecific synthesis of quinolines based upon the rhodium-catalyzed conjugate addition chemistry of aminophenylboronate derivatives. Seventeen different quinolines have been synthesized, with an average yield of 76%. The regiocomplementarity of the reaction to the classical Skraup−Doebner−Von Miller cyclization, coupled with the use of relatively mild, basic reaction conditions and the regiospecificity of the reaction with respect to the synthesis of quinolines substituted in the benzenoid ring combine to make this an attractive method for the synthesis of substituted quinolines. The

(12) Standard experimental procedure: To a suspension of chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.03 equiv), 2-aminophenylboronic acid (2 equiv), and enone (1 equiv) in toluene (ca. 0.19 M) was added 3.8 M KOH (2 equiv). The mixture was stirred vigorously at rt for several hours until TLC indicated complete consumption of enone. The reaction mixture was then transferred to a round bottom flask equipped with a reflux condenser. After the addition of 5% palladium on charcoal (0.2 equiv), the reaction was heated under reflux for 16 h, open to air. After cooling, the mixture was filtered over Celite, washing with five equivalent volumes of toluene. The solvent was removed under reduced pressure and the crude product purified by flash column chromatography.

(13) Baudoin, O.; Guénard, D.; Guérrite, F. *J. Org. Chem.* **2000**, *65*, 9268–9271.

potential extension of this method to the synthesis of heteroaryl-fused pyridines by way of aminoheteroaryl boronate derivatives is an enticing prospect and will be examined in due course.

Acknowledgment. We thank the EPSRC and GlaxoSmithKline (EP/E020712/1) for support of this work.

Supporting Information Available: Experimental protocols for the quinoline syntheses and preparation of the substituted aminophenylpinacolboronates, together with full compound characterization data and $^{1}H/^{13}C$ NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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