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Enantioselective Boronate Additions to *N*-Acyl Quinoliniums Catalyzed by Tartaric Acid

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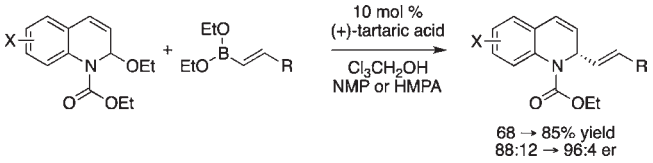
ABSTRACT



Tartaric acid catalyzes the asymmetric addition of vinylboronates to *N*-acyl quinoliniums, affording highly enantioenriched dihydroquinolines. The catalyst serves to activate the boronate through a ligand-exchange reaction and generates the *N*-acyl quinolinium in situ from the stable quinoline-derived *N,O*-acetal.

Nucleophilic addition to quinolines is an effective method to synthesize dihydroquinolines, useful synthons in the construction of biologically active alkaloids.[1] Shibasaki reported the first catalytic, enantioselective addition to quinoline, a Reissert-type reaction with trimethylsilylcyanide and a bifunctional phosphine-BINOLate catalyst.[2] Alexakis performed a direct lithiation of quinolines in the presence of a chiral diether catalyst.[3] Recently, Takemoto reported a Petasis-type reaction of quinolines with boronic acids and a bifunctional thiourea catalyst.[4] All of these reactions require an *in situ* formation of an *N*-acyl quinolinium generated by the addition of a chloroformate to the quinoline electrophile. We hoped to utilize 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinolines (EEDQs) as stable *N*-acyl quinolinium precursors to avoid the use of chloroformates.[5] Although EEDQs are reactive partners in Petasis-like reactions,[6] only one enantioselective transformation of EEDQs has been reported.[6c] Herein, we report the use of tartaric acid as a catalyst to perform highly enantioselective additions of boronates to *N*-acyl quinoliniums to form chiral dihydroquinolines.

Many of the seminal developments of asymmetric synthesis and catalysis utilize tartaric acid derivatives as chiral auxiliaries or catalysts.[7] The Sharpless asymmetric epoxidation,[8] asymmetric allylborations,[9] and asymmetric Diels–Alder reactions[10] are just a few examples of highly utilized

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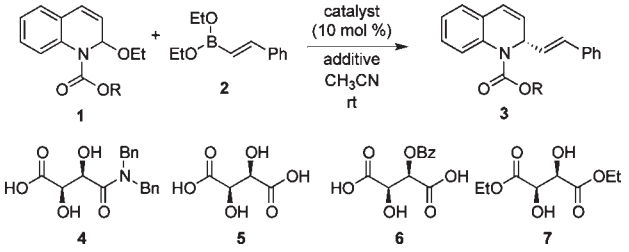
transformations employing the tartaric acid motif. Surprisingly, tartaric acid itself has found little use as an organocatalyst despite its ubiquitous nature and densely functionalized structure.[11] Instead, the role of tartaric acid in asymmetric synthesis is most often as a resolving agent.[12]

Table 1. Asymmetric Addition of Boronates to EEDQs[a]

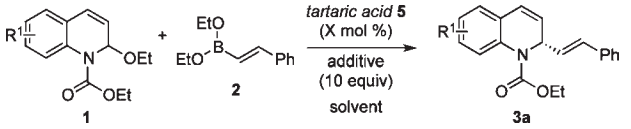


entry	R	catalyst	additive (equiv)	solvent	yield[b]	er[c]
1	Et	**4**	$Yb(OTf)_3$ (0.05)	EtOAc	24%	54:46
2	Et	**5**	$Yb(OTf)_3$ (0.1)	EtOAc	13%	56:44
3	Et	**5**	–	EtOAc	21%	69:31
4	Et	**5**	–	CH_3CN	31%	75:25
5	Et	**5**	EtOH (1.0)	CH_3CN	21%	74:26
6	Et	**5**	PhOH (1.0)	CH_3CN	27%	80:20
7	Et	**5**	AcOH (1.0)	CH_3CN	10%	75:25
8	Et	**5**	CF_3CH_2OH (1.0)	CH_3CN	46%	81:19
9	Et	**6**	CF_3CH_2OH (1.0)	CH_3CN	8%	62:38
10	Et	**7**	CF_3CH_2OH (1.0)	CH_3CN	18%	50:50
11	Et	**5**	CF_3CH_2OH (10.0)	CH_3CN	73%	83:17
12	CH_3	**5**	CF_3CH_2OH (10.0)	CH_3CN	59%	77:23
13	Bn	**5**	CF_3CH_2OH (10.0)	CH_3CN	36%	72:28
14	Ph	**5**	CF_3CH_2OH (10.0)	CH_3CN	12%	65:35

[a] Reactions were run with 0.20 mmol of **1**, 0.4 mmol of **2**, 10 mol % catalyst, and additive in solvent (1.0 mL) for 16 h at room temperature under Ar, followed by flash chromatography on silica gel. [b] Yield of isolated product. [c] Enantiomeric ratios determined by HPLC analysis using a chiral stationary phase.

We began our studies using a Lewis acid–Brønsted acid catalyst system of 10 mol % tartramide **4** and 5 mol % $Yb(OTf)_3$, which was previously successful in catalyzing the addition of boronates to 2*H*-chromene acetals.[13] The commercially available EEDQ **1** and diethyl styrylboronate **2** afforded the desired product **3** in 24% yield and 54:46 er under these conditions (Table 1, entry 1). Switching to tartaric acid **5** and 10 mol % $Yb(OTf)_3$ gave a similar result (entry 2); however, omitting the Lewis acid cocatalyst led to increased enantioselectivity (entries 3 and 4). To increase catalyst turnover, protic additives were employed in the reaction (entries 5–7), and it was found 1 equiv of CF_3CH_2OH increased the yield to 46% with a concomitant increase in enantioselectivity of 81:19 er (entry 8).[14] Use of 10 equiv of CF_3CH_2OH gave a 73% yield of **3** and 83:17 er (entry 11). Other tartaric acid derived catalysts, such as the CAB-type catalyst **6** and diethyl tartrate **7**, were tested, but these catalysts did not perform well (entries 9 and 10). Takemoto and co-workers observed that the enantioselectivity of their reaction depended on the type of carbamate.[4] Under the tartaric acid catalyzed conditions, methyl and benzyl substituted carbamates gave slightly lower selectivities and yields relative to the ethyl carbamate (entries 12 and 13). The larger, phenyl-substituted carbamate proved to be the least effective *N*-acyl quinolinium precursor in this reaction (entry 14).

Table 2. Lewis Basic Solvents for the Asymmetric Addition of Boronates to EEDQs[a]



entry	mol % **5**	additive	solvent	temp (°C)	yield[b]	er[c]
1	10	CF_3CH_2OH	THF	20	48%	69:31
2	10	CF_3CH_2OH	Et_2O	20	34%	57:43
3	10	CF_3CH_2OH	DMF	20	9%	83:17
4	10	CF_3CH_2OH	TMU	20	15%	76:24
5	10	CF_3CH_2OH	DMI	20	8%	82:18
6	10	CF_3CH_2OH	DMPU	20	32%	92:8
7	10	CF_3CH_2OH	NMP	20	27%	92:8
8	10	CF_3CH_2OH	HMPA	20	32%	96:4
9	20	CF_3CH_2OH	HMPA	20	49%	95:5
10	20	CF_3CH_2OH	HMPA	-10	63%	93:7
11	20	CCl_3CH_2OH	HMPA	-10	61%	96:4
12	20	CCl_3CH_2OH	HMPA[d]	-10	82%	96:4

[a] Reactions were run with 0.20 mmol of **1**, 0.3 mmol of **2**, 0.02–0.04 mmol of **5**, and 2.0 mmol of additive in solvent (1.0 mL) for 16 h at room temperature under Ar, followed by aqueous workup and flash chromatography on silica gel. [b] Yield of isolated product. [c] Enantiomeric ratios determined by HPLC analysis using a chiral stationary phase. [d] Run for 48 h.

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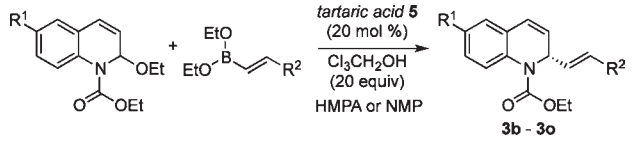
Table 3. Tartaric Acid Catalyzed Addition of Boronates to EEDQs[a]



entry	product	solvent	temp (°C)	yield[b]	er[c]
1	**3b**:R^1=CH_3,R^2=C_6H_5	NMP	-10	81%	94:6
2	**3c**: R^1=OCH_3, R^2=C_6H_5	NMP	-20	74%	94:6
3	**3d**: R^1=Cl, R^2=C_6H_5	HMPA	4	89%	95:5
4	**3e**: R^1=NO_2, R^2=C_6H_5	HMPA	4	73%	92:8
5[d]	**3f**: R^1=AcNH, R^2=C_6H_5	NMP	-10	71%	91:9
6[e]	**3g**: R^1=H, R^2=4-$CH_3OC_6H_4$	HMPA	-10	87%	94:6
7	**3h**: R^1=H, R^2=4-ClC_6H_4	HMPA	-10	86%	92:8
8	**3i**: R^1=H, R^2=3-C_4H_3S	HMPA	-10	83%	96:4
9	**3j**: R^1=H, R^2=3,4-$CH_2O_2C_6H_4$	HMPA	-20	73%	92:8
10	**3k**: R^1=H, R^2=2-Naphthyl	NMP	4	70%	92:8
11	**3l**: R^1=H, R^2=3-FC_6H_4	HMPA	4	77%	95:5
12	**3m**: R^1=Cl, R^2=4-$CH_3OC_6H_4$	HMPA	-20	82%	95:5
13	**3n**: R^1=OCH_3, R^2=4-$CH_3OC_6H_4$	NMP	-20	81%	92:8
14	**3o**: R^1=OCH_3, R^2=3-FC_6H_4	NMP	4	73%	88:12

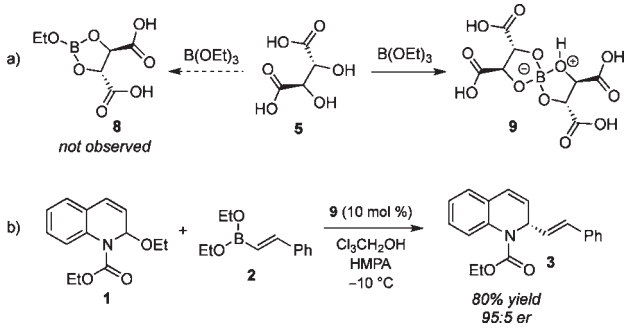
[a] Reactions were run with 0.2 mmol of EEDQ, 0.3 mmol of boronate, 0.04 mmol of **5** and 2.0 mmol of Cl_3CH_2OH in NMP or HMPA (0.4 mL) for 48 h under Ar, followed by aqueous workup and flash chromatography on silica gel. [b] Yield of isolated product. [c] Enantiomeric ratios determined by HPLC analysis using a chiral stationary phase. [d] Entries 5, 10, 11, and 14 were run for 72 h. [e] Entries 6 and 8 were run for 24 h.

Interestingly, increasing the Lewis basicity of the solvent resulted in increased enantioselectivity and yield.[15] Ethereal solvents THF and Et_2O gave lower yields and selectivities than CH_3CN (Table 2, entries 1 and 2). Reactions run in DMF, tetramethylurea (TMU), and 1,3-dimethyl-2-imidazolidinone (DMI) gave low yields but enantioselectivities between 76:24 and 83:17 er (entries 3–5). Strongly coordinating solvents, such as 1,3-dimethyl-tetrahydropyrimidin-2-(1*H*)-one (DMPU), *N*-methylpyrrolidinone (NMP), and hexamethylphosphoramide (HMPA) gave the best selectivity with HMPA, affording dihydroquinoline **3** in 96:4 er (entries 6–8). Increasing the amount of tartaric acid to 20 mol % and lowering the temperature of the reaction increased yields to 63% (entry 9 and 10). Finally, a change to the slightly less acidic CCl_3CH_2OH additive at −10 °C provided the optimal reaction conditions and produced dihydroquinoline **3** in 96:4 er and 82% yield (entry 12).

A substrate table was generated under the optimized reaction conditions using HMPA and NMP as solvent. First, we examined the effect of substitution at the 6-position of EEDQ. Electron-donating groups on EEDQ gave good yields and selectivities in NMP at low temperatures (Table 3, entries 1 and 2), while electron-poor EEDQs required slightly higher temperatures in HMPA (entries 3 and 4). The amido-substituted EEDQ afforded the dihydroquinoline **3f** in 71% yield and 91:9 er (entry 5). The higher reactivity of the electron-rich *N*-acyl quinolinium precursors indicates the importance of stabilizing the positive charge on the electrophilic iminium during the rate-determining step. This trend of reactivity was also observed in the tartaramide-catalyzed additions of boronates to oxocarbeniums.[13]

Next, we expanded the scope of the reaction using functionalized vinylboronates. Electron-donating groups on the boronate gave good results using HMPA with selectivities of >92:8 er (entries 6 and 9). Electron-withdrawing boronates were also good partners in the reaction, with a chlorine-substituted boronate affording product **3h** in 86% yield and 92.5:7.5 er (entry 7). The fluorine substituted boronate reacted slowly and was warmed to 4 °C to afford **3l** in 95:5 er (entry 11). The thiophene-derived boronate gave **3i** in an excellent selectivity of 96.5:3.5 er (entry 8). Difunctionalized products **3m**–**3o** were synthesized in good yields and selectivity, and the reaction appears tolerant of a variety of functionalizations on both the boronate and EEDQ (entries 12–14).

Scheme 1. Catalyst Resting State, Borate **9**



Mechanism studies were undertaken to ascertain the role of the tartaric acid catalyst during the course of the reaction. Although a double exchange reaction occurs between catalyst **5** and boronate **2** the fate of the catalyst after the reaction with the quinolinium remained unclear. To understand whether the tartaric acid would remain free in solution or bound to boron a series of experiments were conducted. Triethyl borate and tartaric acid **5** were mixed in HMPA for 5 min, and an aliquot of the solution was injected into the ESI-MS (Scheme 1a). Monomeric borate **8** was not observed in the reaction, although it is probably a

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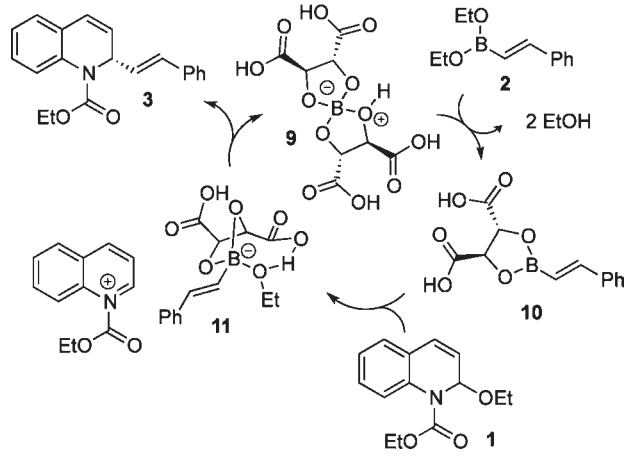
fleeting intermediate in the reaction. Instead a mass was observed for the dimeric tartaric acid adduct **9**, a previously reported tetracoordinated boron "ate" structure.[16] To determine whether boron "ate" **9** is catalytically viable, the complex was formed in situ and used in the reaction (Scheme 1b). Using 10 mol % **9** under the optimized reaction conditions, dihydroquinoline **3** was formed with similar selectivity and yield as the original reaction conditions.

Scheme 2. Proposed Catalytic Cycle



Our proposed catalytic cycle relies on the tetracoordinated boron "ate" **9** as the resting state of the catalyst (Scheme 2). The dimeric borate **9** undergoes a disproportionation with boronate **2** to form the activated alkenyl dioxaborolane **10**. This exchange is likely facilitated by the protic Cl_3CH_2OH additive.[16] Next, activated dioxaborolane **10** reacts with *N*,*O*-acetal **1** to form the *N*-acyl quinolinium and boron "ate" intermediate **11**. Nucleophilic addition of the alkenyl group to the iminium proceeds enantioselectively to furnish dihydroquinoline **3** and regenerate complex **9**.

In summary, we have developed a nucleophilic boronate addition reaction to stable EEDQs to form chiral dihydroquinolines catalyzed by simple, inexpensive tartaric acid. The reaction proceeds with high enantioselectivity, good yield, and excellent functional group tolerance. Mechanism studies indicated that the tartaric acid activates the boronate via a double-exchange reaction, and following the first catalytic cycle the catalyst resting state is a tetracoordinated boron "ate." While often overlooked as a catalyst in favor of its many derivatives, tartaric acid was found to be a competent diol-exchange catalyst and the optimal catalyst in this particular reaction. Further studies into the application of tartaric acid in organocatalysis are ongoing.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.