Asymmetric Catalysis

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Enantioselective Addition of Boronates to Acyl Imines Catalyzed by Chiral Biphenols**

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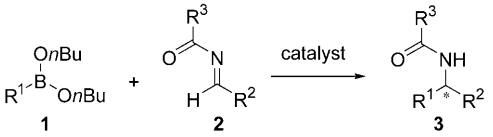
Chiral biphenols are privileged catalyst structures[1] utilized in a wide range of reactions which continues to expand.[2] The accessibility of the chiral framework and structural variants is a key aspect of the utility this class exhibits in asymmetric catalysis.[3] More recently, chiral biphenol catalysts have proven to be effective catalysts for asymmetric conjugate addition reactions, the asymmetric allylboration of ketones[4] and acyl imines,[5] as well as the asymmetric three component Petasis condensation reaction of secondary amines, glyoxylates, and alkenyl boronates.[6] An important mechanistic facet in each of the reactions is the exchange of one of the boronate alkoxy groups with the biphenol to create a more reactive boronate species.[4,7] We sought to expand the repertoire of boronate nucleophiles that will react with acyl imines using chiral biphenol catalysts. Our approach towards the rapid identification of the optimal catalyst for each nucleophilic addition reaction was to screen a collection of chiral biphenols.[8] Screening chiral catalyst collections has proven to be an effective method for catalyst identification[9] and reaction discovery.[10] In this approach the efficient identification of the optimal catalyst is maximized and unexpected results or patterns in reactivity can be rapidly elucidated. Herein we describe the identification and application of chiral biphenol catalysts for the addition of aryl, vinyl, and alkynyl boronates to acyl imines by a catalyst screening approach.

Our investigations began with the identification of reaction conditions that promote the addition of aryl, vinyl, and alkynyl boronates to acyl imines [Eq. (1)]. For each boronate, the nucleophilic addition proceeded only by the inclusion of a biphenol catalyst; a yield of less than 5% was obtained in the absence of any biphenol catalyst. In developing a general protocol for a catalyst screening process, the di-*n*-butyl boronate was determined to be optimal because of its hydrolytic stability. Good yields could be obtained for each of the nucleophiles using binol (binol = 2,2'-dihydroxy-1,1'-binaphthyl) as the catalyst. The next step was to perform a screen by using a collection of chiral biphenol catalysts in each of the boronate addition reactions. Twelve chiral biphenols were screened as catalysts (Figure 1a) in the presence of benzoyl imine **7** and the aryl, alkenyl, and alkynyl boronates **6**, **9**, and **11** respectively (Figure 1b). Comparing the enantiomeric ratio of each nucleophile as a function of the catalyst employed illustrated notable trends (Figure 1c). The use of catalyst **4b** with aryl nucleophile **6** yielded the desired diaryl amide with excellent selectivity, whereas use of catalyst **4b** in the presence of alkenyl boronate **9** or alkynyl nucleophile **11** afforded the corresponding product in lower selectivities. In each case, a different binol catalyst structure proved to be the most effective for each boronate nucleophile. However, a catalyst was identified that afforded the addition product in greater than 95:5 enantiomeric ratio for each of the boronate nucleophiles investigated.



(1)

The scope of the reaction was investigated for each of the boronate nucleophiles. In general, the optimal catalyst identified in the screening experiments, **4b**, proved effective for all of the aryl boronates evaluated in the reaction. Aryl boronates (Table 1, entries 1–6), aryl (Table 1, entries 7–8) and aliphatic (Table 1, entry 9) imines, as well as acyl imine substituents (Table 1, entries 10–12) were found to be effective in the biphenol-catalyzed addition reaction, each affording the corresponding amide in good yields (> 70% yield of the isolated product) and enantioselectivities (> 95:5 e.r.).

Vinyl boronates (Table 2, entries 1–5) also afforded the corresponding allylic amide products in high yield and selectivity. Catalyst **4d** also promoted the vinyl addition to a series of substituted aryl, heteroaryl, and alkyl imines (Table 2, entries 6–8) as well as substituted acyl imines (Table 2, entries 9–11) in good yields and selectivities (> 70% yield, > 95:5 e.r.).

Similarly, substituted alkynyl boronates (Table 3, entries 1–6) proved successful as the desired propargyl amides were isolated in high yield and selectivity. Aryl, heteroaryl, and aliphatic (Table 3, entries 7–9), as well as acyl-substituted imines (Table 3, entries 10 and 11) produced the desired products in good yields and selectivities by using catalyst **5d**.

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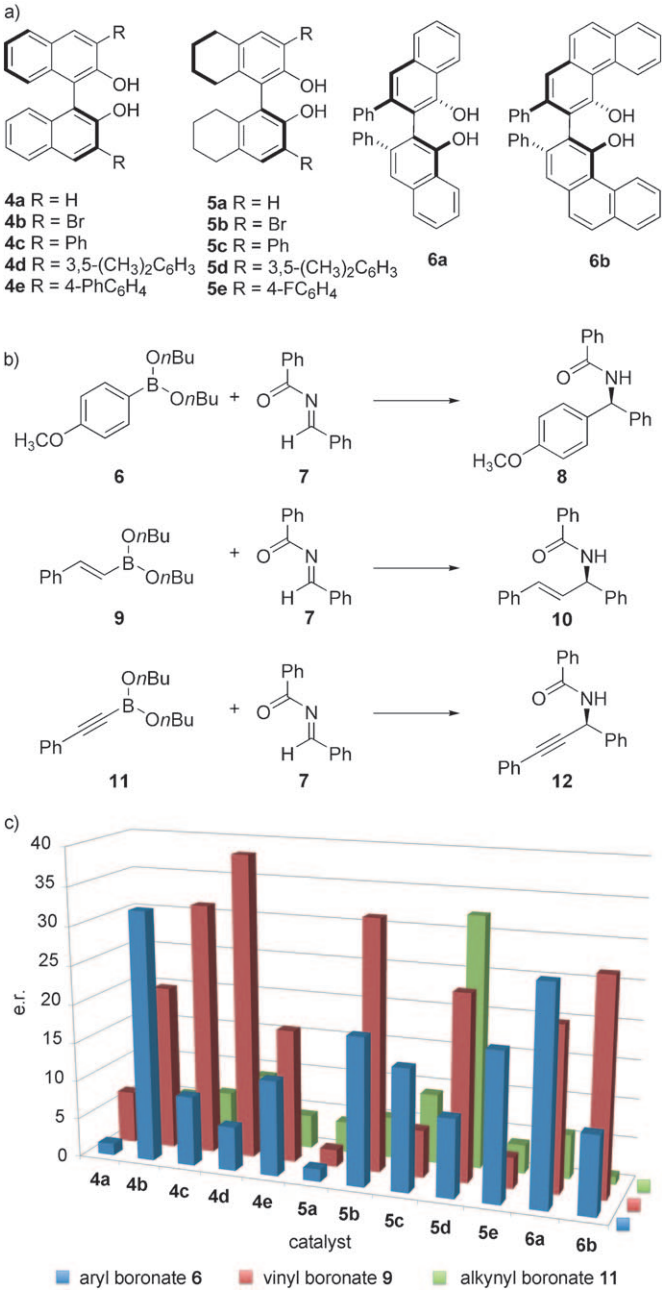
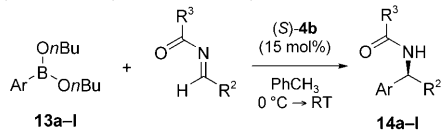
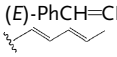


Figure 1. a) Chiral biphenols. b) Nucleophilic boronate reactions promoted by chiral biphenols. c) Catalyst screen for enantioselectivity.

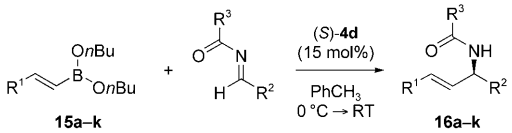
Table 1: Asymmetric arylboration of acyl imines.[a]

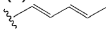


Entry	Ar	R^2	R^3	Yield [%][b]	e.r.[c]
1	4-CH_3OPh	Ph	Ph	80	98:2
2	4-CH_3Ph	Ph	Ph	82	98:2
3	3,4-OCH_2OPh	Ph	Ph	91	96:4
4	4-BrPh	Ph	Ph	95	99:1
5	2-BrPh	Ph	Ph	72	97:3
6	4-ClPh	Ph	Ph	98	98:2
7	4-CH_3OPh	4-BrPh	Ph	80	98.5:1.5
8	4-CH_3OPh	2-C_4H_3S	Ph	89	96:4
9	4-CH_3OPh	Cy	Ph	70	95.5:4.5
10	4-CH_3OPh	Ph	(*E*)-PhCH=CH	87	98:2
11	4-CH_3OPh	Ph		83	98:2
12	4-CH_3OPh	Ph	Cy	71	97.5:2.5

[a] Reaction conditions: catalyst **4b** (0.0375 mmol), arylboronate (0.25 mmol), and acyl imine (0.25 mmol) in toluene (2.5 mL) for 18 h at 0 °C→RT. [b] Yield of isolated product. [c] Determined by chiral HPLC methods. Cy = cyclohexyl.

Table 2: Asymmetric vinylboration of acyl imines.[a]

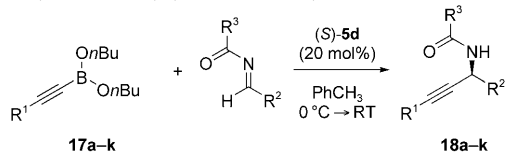


Entry	R^1	R^2	R^3	Yield [%][b]	e.r.[c]
1	Ph	Ph	Ph	85	97.5:2.5
2	2-C_4H_3S	Ph	Ph	88	99:1
3	3-FPh	Ph	Ph	82	96.5:3.5
4	4-CH_3OPh	Ph	Ph	83	96:4
5	Cy	Ph	Ph	75	98:2
6	Ph	4-Br-Ph	Ph	80	95.5:4.5
7	Ph	2-C_4H_3S	Ph	91	95:5
8	Ph	*c*-C_6H_{11}	Ph	74	95.5:4.5
9	Ph	Ph	(*E*)-CH=CHPh	87	98.5:1.5
10	Ph	Ph		83	97.5:2.5
11	Ph	Ph	Cy	82	97.5:2.5

[a] Reaction conditions: catalyst **4d** (0.0375 mmol), alkenyl boronate (0.25 mmol), and acyl imine (0.25 mmol) in toluene (2.5 mL) for 18 h, 0 °C→RT. [b] Yield of isolated product. [c] Determined by chiral HPLC methods.

We continued our studies by characterizing the boronate species under the catalytic reaction conditions. Electron-spray ionization mass spectrometry (ESI-MS) experiments of reaction mixtures at room temperature containing binol-derived diols and boronates in the presence and absence of benzoyl imine **7,** were conducted. ESI-MS is an effective process for the characterization of intermediates that are otherwise difficult to characterize by purification.[11,5] The mixture of binol **4b** and boronate **9** was analyzed by using a MicroMass ZQ 2000 mass spectrometer in positive electrospray ionization mode. Under these conditions the mass of a boronate resulting from exchange of one of the alkoxy groups with binol **4b** was observed, without any detectable formation of the corresponding cyclic boronate, consistent with previous results obtained for the allylboration reaction. Furthermore, the use of the chiral cyclic boronate derived from binol **4b** and the boronate **9** resulted in low yield (<20%) and low enantioselectivity (55:45 e.r.) when reacted with imine **7** under the same reaction conditions. Although computational studies have implicated the formation of cyclic boronates under catalytic conditions,[12] the experimental results obtained to date demonstrate an acyclic boronate complex

Table 3: Asymmetric alkynylboration of acyl imines.[a]



Entry	R^1	R^2	R^3	Yield [%][b]	e.r.[c]
1	Ph	Ph	Ph	99	96:4
2	4-FPh	Ph	Ph	76	93:7
3	3-C_4H_3S	Ph	Ph	72	94:6
4	*n*-hexyl	Ph	Ph	90	92:8
5	$Ph(CH_2)_2$	Ph	Ph	71	97:3
6	*i*-propenyl	Ph	Ph	80	96:4
7	Ph	4-CH_3OPh	Ph	99	96:4
8	Ph	4-BrPh	Ph	62	93:7
9[d]	Ph	2-C_4H_4S	Ph	80	97:3
10	Ph	Ph	4-BrPh	70	97:3
11	Ph	Ph	4-OCH_3Ph	69	95:5

[a] Reaction conditions: catalyst **4d** (0.023 mmol), alkynyl boronate (0.115 mmol), acyl imine (0.115 mmol) in toluene (1 mL) for 36 h, 0 °C→RT. [b] Yield of isolated product. [c] Determined by chiral HPLC methods. [d] Reaction run with 3 equivalents of alkynyl boronate.

under catalytic conditions. The stereochemical model developed for the reaction of the boronate complex with acyl imines is consistent with the observed stereoinduction (Figure 2). The observed enantiofacial selectivity is the

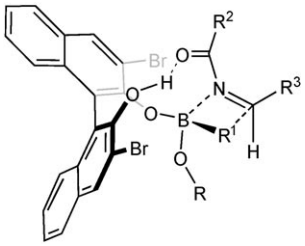
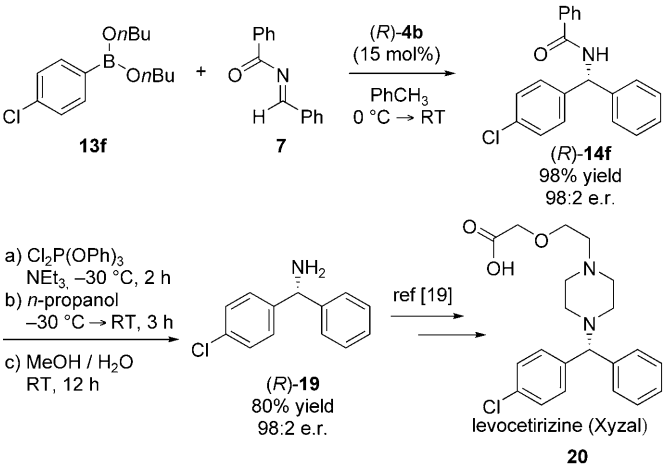


Figure 2. Proposed transition state for asymmetric boronate addition to acyl imines.

result of catalyst coordination to the *Z* conformer of the acyl imine. The more reactive *Z* conformer has been proposed by Corey et al.[13] and others[14] in reactions involving imines because of the steric interactions that arise from the metal reagent and the substituents of the imine. The hydrogen-bonding character of the biphenol activates the acyl imine towards nucleophilic attack and orients the boronate complex towards *Re* enantiofacial selectivity in the addition reaction.[5]

Lastly, the methodology was utilized in the synthesis of the known antihistamine levocetirizine (Xyzal). The construction of amine (*R*)-**19** is a key step in the synthesis.[15–17] Our approach to this desired intermediate used (*R*)-**4b** as the catalyst and aryl boronate **13f** to afford diaryl amide **14f** in 98% yield upon isolation and 98:2 e.r. (Scheme 1). Removal of the acyl protecting group was accomplished using a method recently described by Prati et al.,[18] resulting in the production of free amine (*R*)-**19** in 80% yield with complete



Scheme 1. Synthesis of the key intermediate in the formal synthesis of Xyzal.

retention of stereochemistry constituting a formal synthesis of Xyzal (**20**).[19]

In summary, we have applied a chiral biphenol catalyst screening protocol for the rapid identification of enantioselective catalytic reactions. The approach successfully identified a unique catalyst that promoted the reaction enantioselectively for each of the boronates investigated. Furthermore, the optimal catalyst identified proved general for each class of boronate nucleophiles. Mechanistic studies demonstrate that there is an exchange between the boronate and catalyst, giving rise to the active nucleophilic boronate reagent. The method was utilized in the enantioselective synthesis of the antihistamine Xyzal. Continued investigations include use of the screening approach toward expansion of the scope and utility of the reaction, as well as detailed mechanistic studies.

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