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

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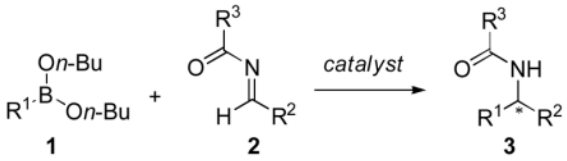
Chiral biphenols are privileged catalyst structures[1] utilized in a wide range of reactions that continues to expand.[2] The accessibility of the chiral framework and structural variants is a key aspect of the utility this class exhibits in asymmetric catalysis.[3] More recently, chiral biphenol catalysts 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 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 via a catalyst screening approach.



(1)

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, < 5% yield 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 due to its hydrolytic stability. Good yields could be obtained for each of the nucleophiles using BINOL as the catalyst. The

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next step was to perform a screen using a collection of chiral biphenol catalysts in each of the boronate addition reactions. Twelve chiral biphenols were screened as catalysts (Figure 1) in the presence of benzoyl imine **7** and the aryl, alkenyl, and alkynyl boronates **6**, **9**, and **11** respectively (Scheme 1). Comparing the enantiomeric ratio of each nucleophile as a function of the catalyst employed illustrated notable trends (Figure 2). 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 >95:5 er for each of the boronate nucleophiles investigated.

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 (entries 1 – 5, Table 1), aryl (entries 6 – 7) and aliphatic (entry 8) imines, as well as acyl imine substituents (entries 9 – 11) were found to be effective in the biphenol-catalyzed addition reaction each affording the corresponding amide in good yields (>70% isolated yield) and enantioselectivities (>95:5 er).

Vinyl boronates (entries 1–5, Table 2) 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 (entries 6–8) as well as substituted acyl imines (entries 9–11) in good yields and selectivities (>70% yield, >95:5 er).

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

We continued our studies by characterizing the boronate species under the catalytic reaction conditions. Electron spray ionization mass spectrometry (ESI-MS) experiments were conducted at room temperature of reaction mixtures containing BINOL-derived diols and boronates in the presence and absence of benzoyl imine **7**. ESI-MS is an effective process for the characterization of intermediates that are otherwise difficult to characterize via purification.[11,5] The mixture of BINOL **4b** and boronate **9** was analyzed 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, use of the chiral cyclic boronate derived from BINOL **4b** and the boronate **9** resulted in low yield (< 20%) and low enantioselectivity (55:45 er) 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 under catalytic conditions. The stereochemical model developed for the reaction of the boronate complex with acyl imines is consistent with the observed stereoinduction (Figure 3). The observed enantiofacial selectivity is the result of catalyst coordination to the Z-conformer of the acyl imine. The more reactive Z-conformer has been proposed by Corey[13] and others[14] in reactions involving imines due to 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.[15,16,17] Our approach to this desired intermediate used (*R*)-**4b** as the catalyst and aryl boronate **13f** to afford diaryl amide **14f** in 98% isolated yield and 98:2 er. Deprotection of the amide was accomplished using a method recently described by Prati[18] resulting in the production of free amine **19** in 80% yield with complete 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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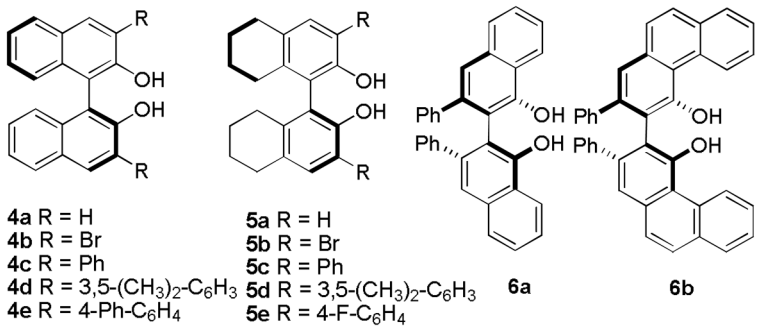


Figure 1.
Chiral Biphenols

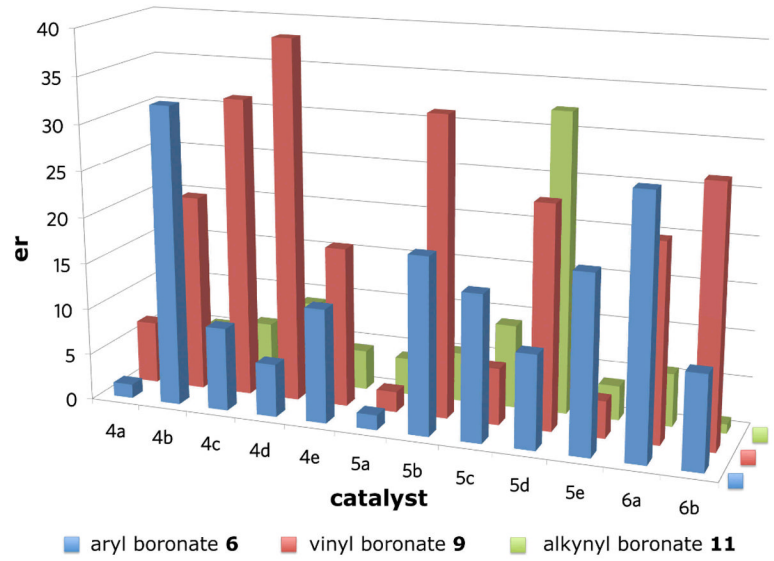


Figure 2.
Catalyst Screen for Enantioselectivity

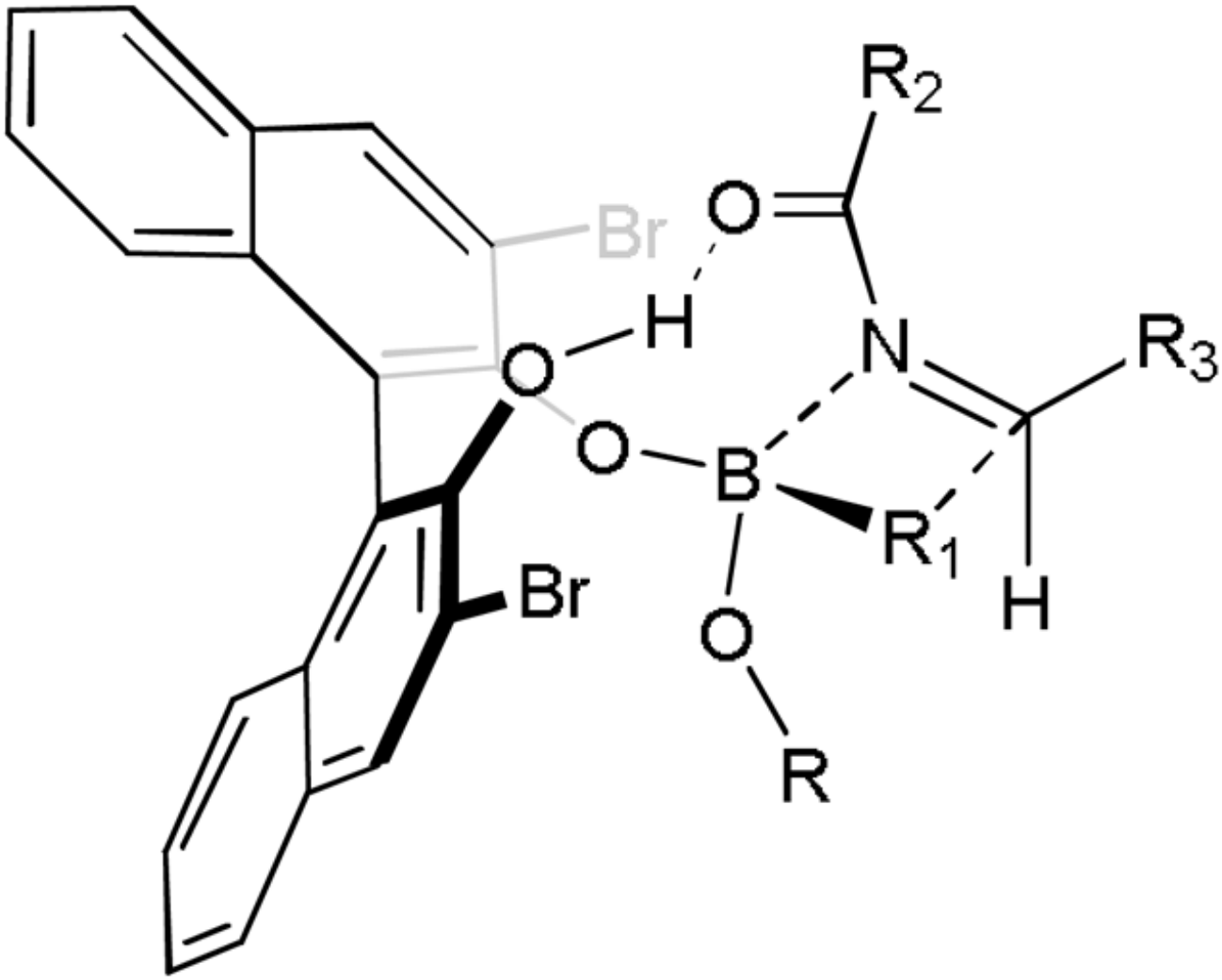
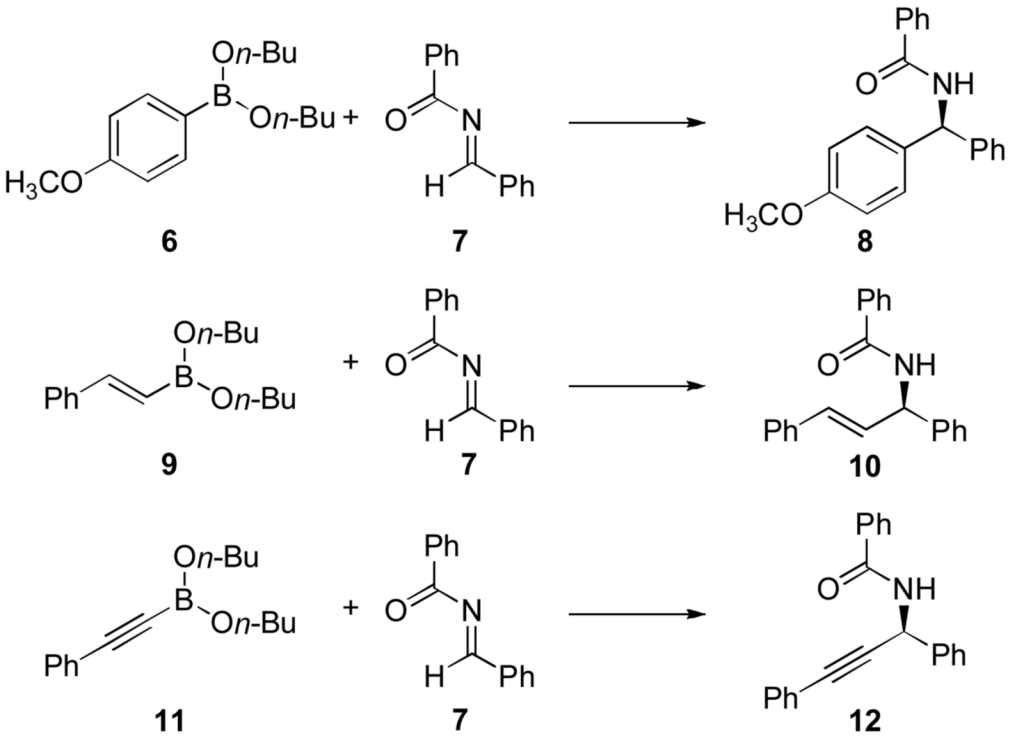
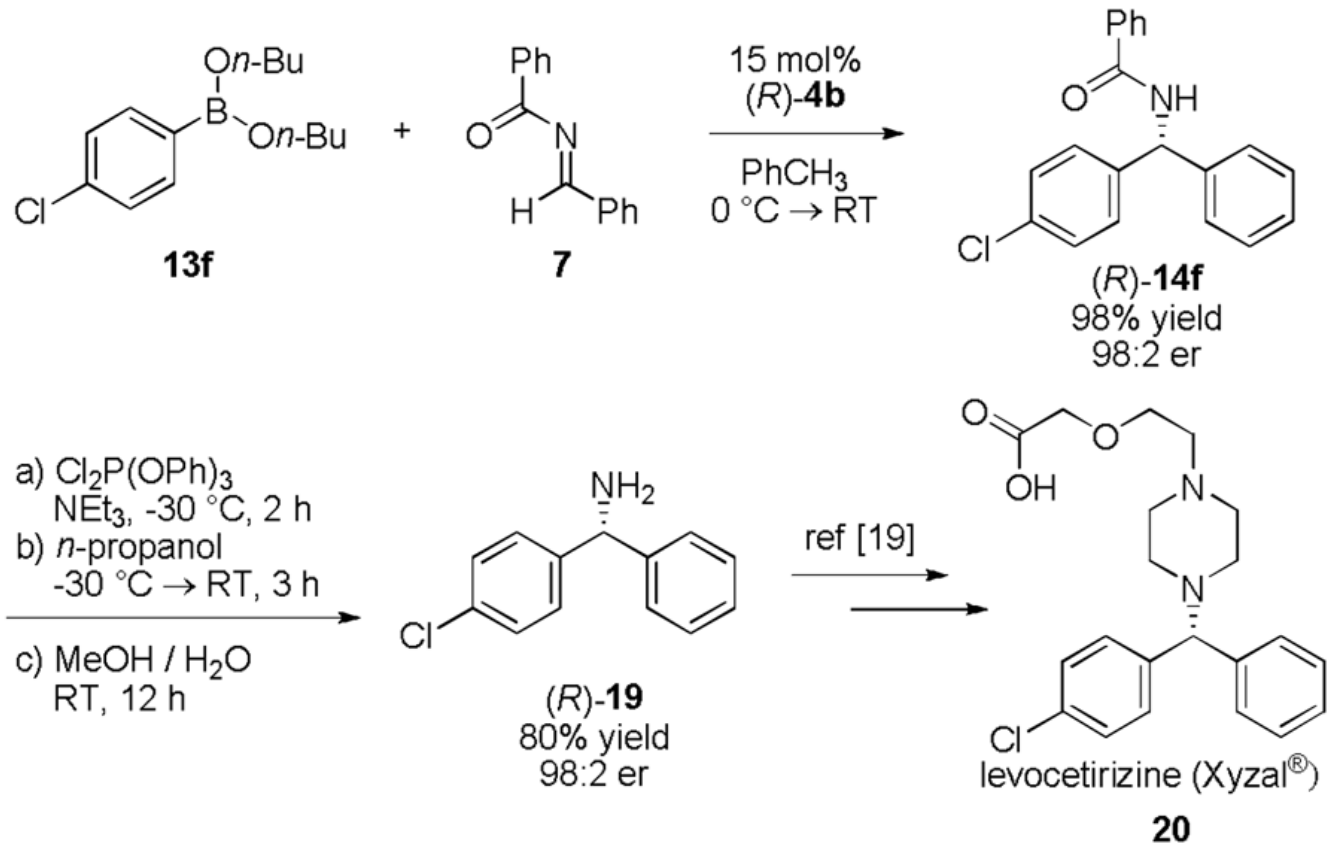


Figure 3.
Proposed Transition State for Asymmetric Boronate Addition to Acyl Imines



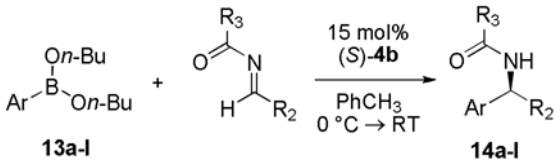
Scheme 1.
Nucleophilic Boronate Reactions Promoted by Chiral Biphenols.



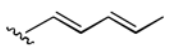
Scheme 2.
Synthesis of key intermediate in the formal synthesis of *Xyzal*®

Table 1

Asymmetric Arylboration of Acyl Imines[a]



13a-l **14a-l**

entry	Ar	R_2	R_3	yield[b]	er[c]
1	4-CH_3O-Ph	Ph	Ph	80	98:2
2	4-CH_3-Ph	Ph	Ph	82	98:2
3	3,4-OCH_2O-Ph	Ph	Ph	91	96:4
4	4-Br-Ph	Ph	Ph	95	99:1
5	2-Br-Ph	Ph	Ph	72	97:3
6	4-Cl-Ph	Ph	Ph	98	98:2
7	4-CH_3O-Ph	4-Br-Ph	Ph	80	98.5:1.5
8	4-CH_3O-Ph	2-C_4H_3S	Ph	89	96:4
9	4-CH_3O-Ph	*c*-C_6H_{11}	Ph	70	95.5:4.5
10	4-CH_3O-Ph	Ph	(*E*)-PhCH=CH	87	98:2
11	4-CH_3O-Ph	Ph		83	98:2
12	4-CH_3O-Ph	Ph	*c*-C_6H_{11}	71	97.5:2.5

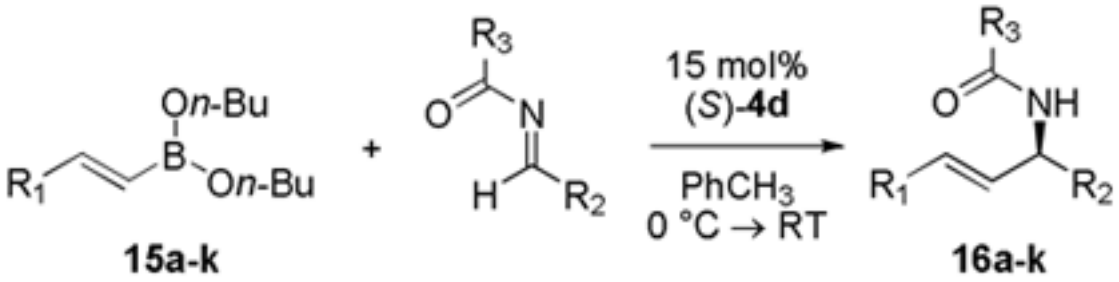
[a] Reactions were run with 0.0375 mmol catalyst **4b**, 0.25 mmol arylboronate, and 0.25 mmol acyl imine in 2.5 mL toluene for 18h at 0 °C → RT.

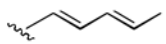
[b] Isolated yields.

[c] Determined by chiral HPLC.

Table 2

Asymmetric Vinylboration of Acyl Imines[a]



entry	R_1	R_2	R_3	yield[b]	er[c]
1	Ph	Ph	Ph	85	97.5:2.5
2	2-C_4H_3S	Ph	Ph	88	99:1
3	3-F-Ph	Ph	Ph	82	96.5:3.5
4	4-CH_3O-Ph	Ph	Ph	83	96:4
5	*c*-C_6H_{11}	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	*c*-C_6H_{11}	82	97.5:2.5

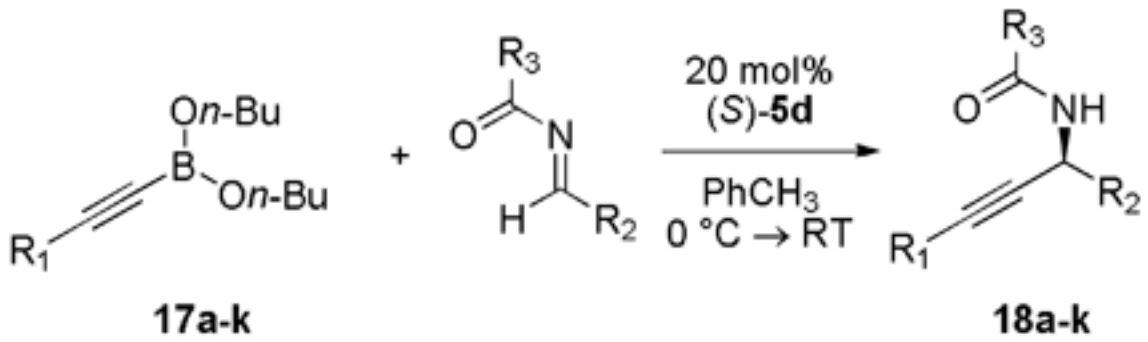
[a] Reactions were set up with 0.0375 mmol catalyst **4d**, 0.25 mmol alkenyl boronate, and 0.25 mmol acyl imine in 2.5 mL toluene for 18h at 0 °C → RT.

[b] Isolated yields.

[c] Determined by chiral HPLC.

Table 3

Asymmetric Alkynylboration of Acyl Imines[a]



17a-k **18a-k**

entry	R_1	R_2	R_3	yield[b]	er[c]
1	Ph	Ph	Ph	99	96:4
2	4-F-Ph	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_3O-Ph	Ph	99	96:4
8	Ph	4-Br-Ph	Ph	62	93:7
9[d]	Ph	2-C_3H_4S	Ph	80	97:3
10	Ph	Ph	4-Br-Ph	70	97:3
11	Ph	Ph	4-OCH_3-Ph	69	95:5

[a] Reactions were set up with 0.023 mmol catalyst **4d**, 0.115 mmol alkynyl boronate, 0.115 mmol and acyl imine in 1 mL toluene for 36 h at 0 °C → RT.

[b] Isolated yields.

[c] Determined by chiral HPLC.

[d] Reaction run with 3 equiv alkynyl boronate