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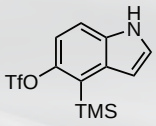

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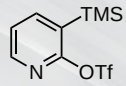

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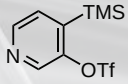

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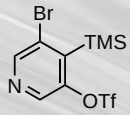

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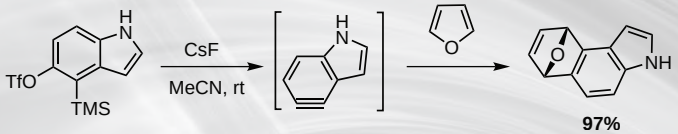

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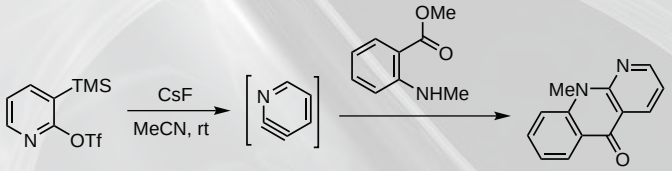

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References:

(1) Im, G-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933.

(2) Goetz, A. E.; Garg, N. K. *Nature Chem.* **2013**, *5*, 54.

(3) Saito, N.; Nakamura, K.; Shibano, S.; Ide, S.; Minami, M.; Sato, Y. *Org. Lett.* **2013**, *15*, 386.

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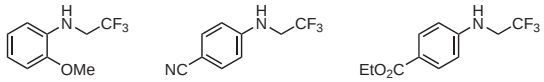

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ABOUT OUR COVER

Detail from ***Lake Albano***. Photo courtesy National Gallery of Art, Washington, DC.

Lake Albano (oil on canvas, 121.9 x 170.4 cm) was completed in 1762 by Richard Wilson (1712/1714–1782). Born and raised in Wales, Wilson left for London at about age 15 to study portraiture under Thomas Wright. After about six years of training, he struck out on his own as a portraitist for almost two decades, but without attaining the recognition and financial success he had hoped for. In 1752, he made a trip to Italy that proved to be a turning point in his career as an artist. In Rome, he came to admire and was heavily influenced by the works of celebrated landscape painters, such as Claude Lorrain and Gaspard Dughet, who had lived and worked in the city a century earlier. In 1757 or 1758, he returned to Britain, where he devoted himself to painting primarily Welsh and Italian (often idealized) sceneries and to training a new generation of artists. The fame and success that eluded him as a portrait artist he attained as a landscape painter. Considered by many to be a pioneer of British landscape painting, Wilson has been an acknowledged strong influence on later British landscapists, in particular John Constable and Joseph Turner.

Lake Albano* embodies many of the elements that characterize Wilson's landscapes: small human figures; a body of water; a building or two, often in the middle ground of the painting; bright and generally clear skies; and delicate trees and foliage, often more prominent in the foreground. His landscapes, whether actual or idealized, depict charming and serene scenes, with human and animal figures inserted to give depth and scale but not distract from the beauty or majesty of the surroundings. While his landscapes tend to capture the general appearances of nature, his rendering of light and distance validate his keen and delicate observations of the natural world.

This painting is part of the Paul Mellon Collection at the National Gallery of Art, Washington, DC.

** Actual Lake Albano was a favorite setting for a number of landscape artists of the 18th and 19th centuries. To find out who else has painted it, visit* ***Aldrich.com/acta472***

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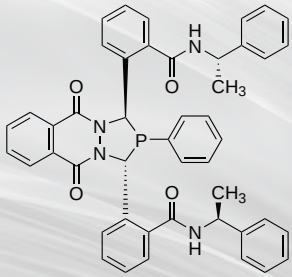

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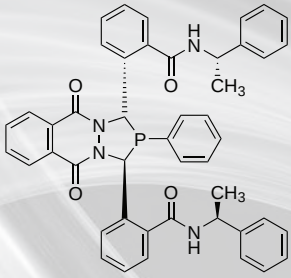

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References:
(1) Clark, T. P.; Landis, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 11792.
(2) Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R.; Abboud, K. A. *Org. Lett.* **2007**, *9*, 2665.

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Highly Enantioselective Hydroformylation of Alkenes by Rhodium-Diazaphospholane Catalysts

Dr. Gene W. Wong
(Deceased)

Prof. Clark R. Landis

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Keywords. asymmetric catalysis; hydroformylation; rhodium; chiral phosphines; organic synthesis.

Abstract. Rhodium-diazaphospholane complexes catalyze the highly enantioselective hydroformylation of aryl alkenes, vinyl acetates and carboxamides, functionalized allylic substrates, heterocycles, and 1,3-dienes at fast rates and high turnover numbers. The state of the art (≥ 90% ee) in enantioselective hydroformylation is reviewed and highlighted with applications to organic synthesis.

Outline

1. Introduction

Chiral aldehydes are versatile intermediates for the construction of complex molecules with applications as fragrances, agrochemicals, pharmaceuticals, natural products, and others. The importance of chiral aldehydes to target-oriented synthesis has long been recognized by organic chemists, and is best summarized in the following statement:[1] "The aldehyde is arguably the most versatile carbonyl functionality…. This unique combination of functional versatility and activity renders chiral aldehydes highly valuable intermediates in asymmetric synthesis". However, chiral aldehydes constitute a synthetically challenging class of building blocks. Common routes to chiral aldehydes include: aldol condensations;[2–6] α-functionalization of aldehydes[7–11] or carbonyl compounds (requires reduction to a formyl group);[12–16] conjugate additions;[17–19] cycloaddition reactions;[20] Friedel–Crafts alkylations;[21] and Mannich condensations.[6] Many of these methods lead to structurally diverse aldehydes, but suffer from drawbacks associated with organocatalysis or the use of stoichiometric chiral auxiliaries: atom-inefficiency, low reaction temperatures and long reaction times, aldehyde side reactions (aldol condensation, epimerization, etc.) especially at non-neutral pHs, and low catalytic activity (<100 turnover numbers (TON); TON = moles of product/moles of catalyst). Perfect atom-economy, inexpensive reactants, neutral reaction conditions, simple purification, fast rates, and high TONs make the rhodium-catalyzed enantioselective hydroformylation an attractive alternative for the scalable synthesis of chiral aldehydes.

Hydroformylation is a large-scale commodity process yielding millions of pounds of linear aldehydes per year from inexpensive alkenes and synthesis gas (carbon monoxide and dihydrogen). In contrast, the rhodium-catalyzed *asymmetric* hydroformylation (AHF) is underutilized due to the limited number of ligands that preferentially form the branched aldehyde with high yield and enantioselectivity. Although the rhodium-catalyzed asymmetric hydroformylation has rapidly advanced in recent years, there are unmet challenges with the current state-of-the-art ligands; these include AHF of substrates such as multisubstituted alkenes; modular ligands for substrate optimization; catalyst-controlled chemo-, regio-, and enantioselectivities; and highly active and robust catalysts.

The catalytic asymmetric *hydrogenation* of C=C and C=X (where X = O or N) with dihydrogen is well established as a powerful method in organic synthesis. Noyori has described asymmetric catalysis as four-dimensional chemistry: Not only is perfect stereochemistry for a molecule (x, y, z) a requisite, but attaining optically active materials in a reasonable amount of time (t) is also paramount.[22] Similar challenges apply to the catalytic AHF. AHF is operationally similar to the asymmetric hydrogenation in that both reactions use gaseous reagents under pressurized conditions. Hydroformylations are commonly performed in autoclaves (150–5000 psi) or glass bottles (15–150 psi). The demand for higher gas pressures in these reactions arises from two factors: (i) the generation of active hydroformylation catalysts, and (ii) the desire to achieve high reaction rates and selectivities. Both of these factors depend on efficient gas–liquid mixing and, for very active catalysts, mass transport of gas is among the limiting factors of the reaction rate. For these reasons, AHF procedures do not commonly use balloons of H_2 and CO. Thus, an important consideration in the application of AHF by a synthetic chemist is the cost and sophistication of the equipment needed. Rhodium-diazaphospholane complexes are highly active and robust enantioselective hydroformylation catalysts that typically operate at mild reaction temperatures and pressures.

Hydroformylation has been thoroughly reviewed.[23–34] This survey offers an in-depth look at the effect of diazaphospholane ligands[35,36] in rhodium-catalyzed enantioselective hydroformylations of structurally

diverse alkenes and comparison to that of existing state-of-the-art ligands (**Figures 1** and **2**). We limit our treatment to reactions that yield >90% enantiomeric excess, that is, reactions of potential interest to modern synthetic chemists. We de-emphasize other important criteria in the evaluation of enantioselective hydroformylation catalysts such as chemoselectivity, regioselectivity, substrate scope, syngas pressure and temperature effects, catalyst activity and speciation, and scalability.

Given the precedent of chiral phosphorus-containing ligands being effectively employed in asymmetric *hydrogenation* catalysis, it is surprising how challenging enantioselective rhodium-catalyzed AHF remained until Takaya, Nozaki, and co-workers reported the ligand (*R,S*)-BinaPhos (**1a**) in 1993.[37] The use of enantioselective hydroformylation in organic synthesis has remained sparse due to the small number of ligands that exhibit desirable selectivity for many alkenes. Herein, a sampling of exceptional results is presented for several substrate classes: aryl alkenes, vinyl acetates and amides, functionalized allylic alkenes, heterocycles, 1,3-dienes, and miscellaneous alkenes. Relevant synthetic applications of enantioselective hydroformylation using diazaphospholane ligands are included throughout this review.

2. Enantioselective Hydroformylation of Alkenes

The relative rates of reactivity of rhodium-catalyzed hydroformylations generally decrease with increased substitution of the alkene (**Figure 3**).[38–40] Terminal alkenes are the most common substrates employed in AHF due to their ease of hydroformylation under mild conditions (low pressures and temperatures). 1,2-Disubstituted alkenes generally require higher temperatures for reasonable rates, resulting in fewer applications in enantioselective hydroformylation. Not surprisingly, higher temperatures are detrimental to the regio- and enantioselectivity of the hydroformylation for many catalyst systems. Few examples of AHF of 1,1-disubstituted alkenes (to β-chiral aldehydes or quaternary aldehydes) have been reported, and no reports of AHF of trisubstituted and tetrasubstituted alkenes have appeared.

2.1. Styrenes and Aromatic Alkenes

Styrenes are common substrates for AHF due to their potential application in the synthesis of pharmacologically active, anti-inflammatory analgesics (ibuprofen, ketoprofen, and naproxen). Takaya, Nozaki, and co-workers reported the earliest examples of rhodium-catalyzed enantioselective hydroformylation of styrene using (*R,S*)- and (*S,R*)-BinaPhos, with *ent*-**1a** providing the branched aldehyde, (*S*)-(+)-2-phenylpropionaldehyde, in 94% ee.[37] Zhang and Yan developed a related phosphine-phosphoramidite ligand (*R,S*)-YanPhos (**1d**) that led to 98% ee of (*R*)-(–)-2-phenylpropionaldehyde.[41] Ligand libraries derived from BinaPhos,[42–44] bisdiazaphospholanes (**12a–d**),[45,46] (*R,R*)-Ph-BPE (**14**),[47] and (*R,S*)-YanPhos (**1d**)[48] demonstrated stereoselectivities generally similar to those of the corresponding parent ligand—although superior results were observed for some specific substrates. Bisphosphites, such as (*2R,4R*)-chiraphite (**7**),[23,24,49,50] and a D-(+)-glucose-derived bisphosphite, **8**,[51] enabled highly regio- (up

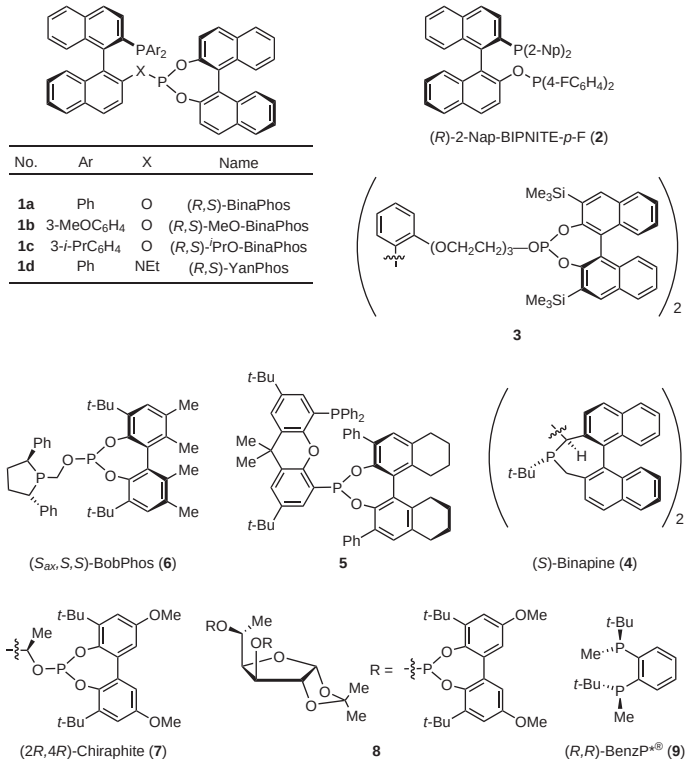


Figure 1. Chiral Phosphorus-Containing Ligands That Exhibit ≥90% ee in the Rhodium-Catalyzed Asymmetric Hydroformylation (AHF) of Various Alkenes.

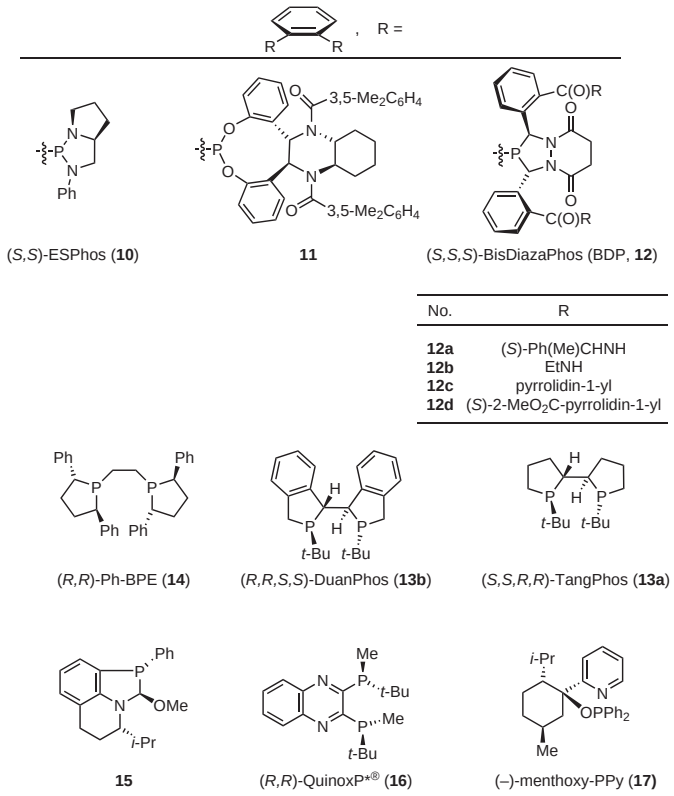


Figure 2. Chiral Phosphorus-Containing Ligands That Exhibit ≥90% ee in the Rhodium-Catalyzed Asymmetric Hydroformylation (AHF) of Various Alkenes.

to 99% branched aldehyde) and enantioselective hydroformylations (90% ee for both ligands) of styrene, albeit at low conversions due to the low reaction temperatures. Hydroformylation of styrene with bisphospholane **14** resulted in 57% conversion and 94% ee.[47,52] Other cyclic bisphosphines, such as (*S*,*S*,*R*,*R*)-TangPhos (**13a**) and Binapine (**4**), yielded less active hydroformylation catalysts (12% conversion in both cases and 90% and 94% ee, respectively).[53] Cobley, Clarke, and co-workers developed BobPhos (**6**), a hybrid phospholane-phosphite ligand, that effected a highly regioselective (98% α-aldehyde) and enantioselective hydroformylation (91% ee) of styrene.[54] AHF with partially optimized conditions using (*S*,*S*,*S*)-bisdiazaphospholane **12a** (bis[(*S*,*S*,*S*)-DiazaPhos]-SPE) achieved a highly regioselective and enantioselective hydroformylation of styrene (98% branched and 93% ee).[55] It is worth noting that carbon monoxide pressure and temperature effects on the regio- and enantioselectivity of the hydroformylation prompted our group to carry out mechanistic studies with rhodium-bisdiazaphospholane catalysts.[56–58]

Four ligands from this group have demonstrated effective enantioselective hydroformylation of substituted styrenes and 1,2-disubstituted aryl alkenes (**eq 1**). The highest reported enantioselectivities of various substituted styrenes occur with hybrid ligands: (*R*,*S*)-BinaPhos (**1a**), (*S*,*R*)-YanPhos (*ent*-**1d**), and (S_{ax},*S*,*S*)-BobPhos (**6**). BinaPhos-based ligands gave 86–88% of the branched aldehyde for unfluorinated (entries 1, 3, 8) and 89–96% for fluorinated styrenes (entries 10, 12, and 14), while exhibiting high stereoselectivity (92–98% ee).[37,43] Zhang and co-workers reported >98% ee's for the AHF of various substituted styrenes using (*R*,*S*)-YanPhos (**1d**) (entries 2, 4, 6, 9, 11, and 13).[41,48] Cobley, Clarke, and co-workers achieved 86–90% ee's and >98:2 α:β ratios for three substituted styrenes (e.g., entry 7) and 2-methoxy-6-vinylnaphthalene by employing (S_{ax},*S*,*S*)-BobPhos (**6**).[54] D-(+)-Glucose-derived bisphosphite (**8**) enabled 91% ee and 99:1 α:β regioselectivity at 20 °C (entry 5).[51] AHF of substituted styrenes with (*S*,*S*,*S*)-diazaphospholane ligand **12a** gave >95% regioselectivity for the α-aldehyde and 70–89% ee's (not shown in eq 1) under unoptimized conditions.[55] Hydroformylation of *para*-substituted styrenes using rhodium-diazaphospholane catalysts revealed branched selectivity increased with electron-withdrawing groups (up to 98.5% branched aldehyde). The Hammett-like plot of log(α:β) vs σ_{para} is linear with a positive slope (σ = +0.56, R^2 = 0.93), suggesting a negative charge buildup in the regioselectivity-determining transition state.[55]

The asymmetric hydroformylation of 2-substituted styrenes has been successfully carried out using (*R*,*S*)-BinaPhos (**1a**)[59] and (*S*,*S*,*S*)-diazaphospholane (**12a**)[55] ligands (**eq 2**). Preference for the α-aryl-substituted aldehyde ranged from 92 to 97%, while the stereoselectivity of the major aldehyde was high, in the 92–96% range. Hydroformylation of indene (not shown) gave 88% ee by using (*S*,*R*)-BiphemPhos, a BinaPhos analogue.[42,44] Nozaki and co-workers explored the hydroformylation of vinyl-substituted heteroaromatic alkenes with (*R*,*S*)-MeO-BinaPhos (**1b**). Hydroformylation of 3-vinylfuran[60] and 3-vinylthiophene[61] resulted in 99% and 91% ee, respectively, with good regioselectivity (92% α-aldehyde) for both substrates. AHF of 2-vinylthiophene and 5-methyl-2-vinylthiophene also exhibited high enantio- (93% and 95% ee) and regioselectivity (94% and 95% α-aldehyde) with the same ligand.[61]

2.2. Vinyl Acetate and N-Vinyl Carboxamides

The asymmetric hydroformylation of vinyl acetate and related enols yields protected α-hydroxy aldehydes, which have numerous applications in synthesis. A handful of ligand classes have achieved the rhodium-catalyzed hydroformylation of vinyl acetate with greater than 90% ee (**eq 3**). These ligands include (*R*,*S*)-BinaPhos (**1a**),[37] (*S*,*S*,*S*)-diazaphospholane ligand **12a**[45] {which generates a highly active catalyst (TOF 19,400 h^{-1}) in the presence of [Rh(acac)$(CO)_2$]},[62] (*R*,*S*)-YanPhos (**1d**)[41] and analogues.[48] It is worth noting that changing the steric bulk of the substituent R had a minimal effect on the selectivity of the hydroformylation, as demonstrated with (*R*,*S*)-BinaPhos (**1a**)[43]

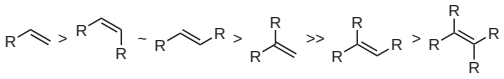
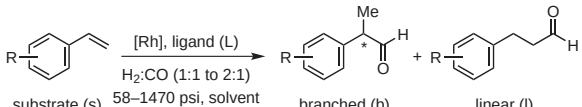


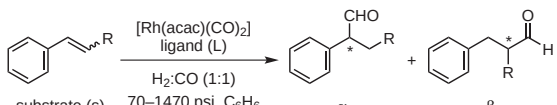
Figure 3. Decreasing Relative Rates of Reactivity of Various Substituted Alkenes in the Rhodium-Catalyzed Hydroformylation. *(Ref. 38–40)*



Entry	R	L	b:l	*R/S*	ee	*Ref.*
1	4-Me	*ent*-**1a**	86:14	(+)	95%	*37*
2	4-Me	**1d**	87:13	*R*	99%	*41*
3	4-*i*-Bu	*ent*-**1a**	88:12	*S*	92%	*43*
4	4-*i*-Bu	**1d**	89:11	*R*	98%	*41*
5	4-MeO	**8**	99:1	(–)	91%	*51*
6	4-MeO	**1d**	86:14	*R*	98%	*41*
7	4-MeO	**6**	98:2	----	90%	*54*
8	4-Cl	*ent*-**1a**	87:13	(+)	93%	*43*
9	4-Cl	**1d**	87:13	*R*	98%	*41*
10	4-F	**1a**	89:11	(–)	92%	*43*
11	4-F	**1d**	88:12	*R*	98%	*41*
12	2-F	**1a**	91:9	(–)	95%	*43*
13	2-F	**1d**	91:9	*R*	98%	*41*
14	(i)	**1a**	96:4	*R*	98%	*43*
15	(ii)	**1c**	94:6	*R*	95%	*44*
16	(ii)	**12a**	98:2	*R*	94%	*55*
17	(iii)	**12a**	98:2	*R*	96%	*55*

[Rh] = [Rh(acac)$(CO)_2$]
(i) = $F_5CCH{=}CH_2$
(ii) = 2-NpCH=CH_2
(iii) = 2-MeO-6-(CH=CH_2)Np

eq 1



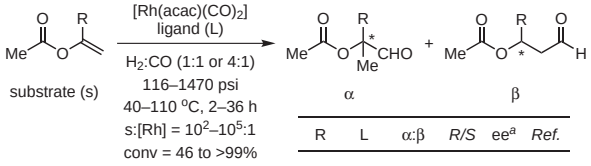
R	L	α:β	*R/S*	ee[a]	*Ref.*
trans-Me	**1a**	>97:3	*R*	92%	*59*
cis-Me	**12a**	92:8	*R*	92%	*55*
cis-Ph	**12a**	-----	*R*	93%	*55*
b	**1a**	96:4	(–)	96%	*59*

[a] ee of the α isomer. [b] s = dihydronaphthalene.

eq 2

and (*R*,*S*)-YanPhos (**1d**)[48] (85–96% regioselectivity for the branched aldehyde and 90–98% ee's). Additional ligands successfully employed in the AHF of vinyl acetate include the diazaphospholidine ESPhos (**10**),[63] the C_2-symmetric bisphosphonite ligand **11**,[64] and supramolecular bisphosphite ligand **3** possessing a long polyether bridge.[65] Buchwald and Wang have demonstrated the effective asymmetric hydroformylation of a 1,1-disubstituted vinyl acetate (where R = CF_3) using ligands **16** and **13b**, and isolated, after oxidation, the corresponding carboxylic acid, 2-trifluoromethyllactic acid, with 99% ee.[66]

Thomas, Klosin, and co-workers have reported 150–180-gram-scale hydroformylations of vinyl acetate using rhodium-diazaphospholane catalysts, whereby remarkable TONs of up to 100,000 and TOFs approaching 20,000 h^{-1} were achieved.[62] Both enantiomers of the α-aldehyde were obtained in excellent purity (>99.0% regioselectivity and 94–96% ee) and utilized in the synthesis of an amino alcohol, an imidazole, and isoxazolines. These syntheses demonstrate that α-hydroxy aldehydes obtained by AHF can be utilized for the synthesis of enantioenriched heterocycles without racemization of the stereocenter.



R	L	α:β	*R/S*	ee[a]	*Ref.*
H	**1a**	86:14	*S*	92%	*37*
H	**12a**	96:4	*S*	96%	*62*
H	**1d**	93:7	*S*	96%	*48*
H	**10**	94:6	*S*	90%	*63*
H	**11**	98:2	*S*	91%	*64*
H	**3**[b]	>99:1	*S*	90%	*65*
F_3C[c]	**16**	----	----	>99%	*66*
F_3C[c]	**13b**	----	----	>99%	*66*

[a] ee of the α isomer. [b] Cs[B(3,5-$(F_3C)_2C_6H_3)_4$] or CsBArF was used as additive. [c] ee is of the corresponding acid, 2-trifluoromethyllactic acid.

eq 3

Burke and Risi have employed bisdiazaphospholane **12a** for the asymmetric hydroformylation of a 1,2-disubstituted (*Z*)-vinyl ester, derived from (*2R*)-8-nonyn-2-ol, for the synthesis of (+)-patulolide C (**Scheme 1**).[67] The enantiomerically enriched α-hydroxy aldehyde obtained from the AHF was treated with Bestmann's ylide to give acetylated (+)-patulolide C. Enzymatic ester hydrolysis completed the synthesis, which was thus effected in three steps and 49% overall yield from (*2R*)-8-nonyn-2-ol. We have demonstrated one-pot AHF and Wittig olefination (WO) sequences for the synthesis of γ-chiral α,β-unsaturated carbonyl compounds. Importantly, olefination with stabilized Wittig reagents proceeds without erosion of the aldehyde enantiopurity.[68] Polyester oligomers and other complex products that contain various functionalities, multiple C–C double bonds, and multiple stereocenters can be made by iterative AHF–WO reactions that employ only a single loading of robust rhodium-diazaphospholane catalysts.

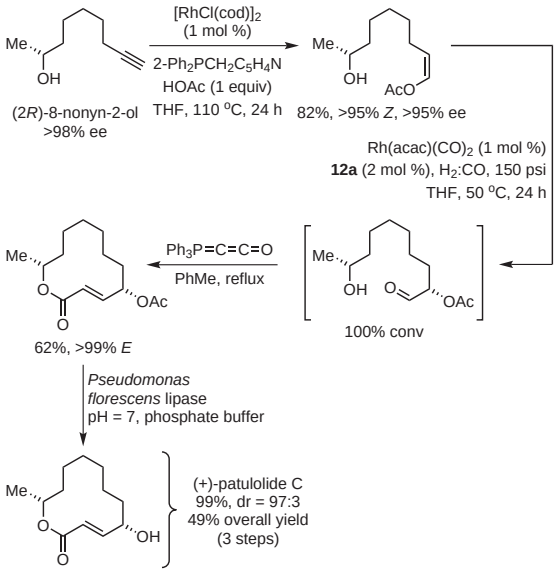
The enantioselective hydroformylation of *N*-vinyl amides in the presence of (*S*,*S*,*S*)-bisdiazaphospholane **12a** and [Rh(acac)$(CO)_2$] leads to the formation of 1,2-amino aldehydes with quantitative conversion and high enantioselectivity (**eq 4**).[69] As was observed in the AHF of vinyl carboxylates, the steric bulk of the carboxamide group had a minimal effect on the regio- and enantioselectivity of the reaction. The hydroformylation of (*Z*)-1-acetamido-1-propene, a 1,2-disubstituted alkene (a commonly difficult substrate class in AHF), yields the corresponding 1,2-amino aldehyde in 90% ee under mild conditions. In contrast, AHF of the (*E*)-1,2-disubstituted alkene (not shown) resulted in poor regio- (α:β ratio = 82:18) and enantioselectivities (32% ee).

2.3. Functionalized Allylic Substrates

Enantioselective hydroformylation of functionalized allylic substrates yields aldehydes that constitute useful building blocks for organic synthesis. Control of the regioselectivity in the hydroformylation of this substrate class has been a challenge for rhodium-coordinated ligands. Approaches that have been employed to mitigate this challenge include the use of substrate-tethered ligands (i.e., "directing groups" and "scaffolding ligands")[70,71] or taking advantage of supramolecular interactions (or secondary coordination sphere interactions) between a substrate and a metal complex outside of primary coordination sphere,[72] which overrides the intrinsic regioselectivity.

A particular aim in this area has been the hydroformylation of allyl cyanide to yield the corresponding α-aldehyde, which is a key building block[73,74] in the synthesis of two important, pharmacologically active targets: a gonadotropin releasing hormone (GnRH) antagonist[75] and a tachykinin NK_1 receptor antagonist.[76,77] A number of the ligands shown in Figures 1 and 2 have proven effective (>90% ee) in the hydroformylation of allyl cyanide: (*R*,*R*)-Ph-BPE (**14**) (96% conv, 90% ee),[52] **13a** (61% conv, 88:12 α:β ratio, and 93% ee),[53] Binapine (**4**) (87% regioselectivity and 94% ee),[53] YanPhos (**1d**) (>99% conv, 96% ee),[48] and **12a** (87% ee, unoptimized conditions).[52]

Zhang and co-workers have investigated the AHF of a series of *N*-allylamides (*N*-allyl carbamates, benzamide, sulfonamides, phthalimide), and obtained modest-to-good regioselectivities (66–

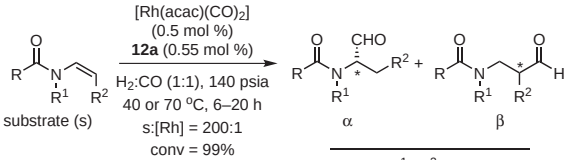


Scheme 1. Concise, Three-Step Synthesis of (+)-Patulolide C with AHF of a 1,2-Disubstituted (*Z*)-Vinyl Ester as the Key Step. *(Ref. 67)*

84% of the α-aldehyde) and high enantioselectivities (92–99% ee's) with YanPhos (**1d**).[78] By comparison, AHF of $CbzNHCH_2CH=CH_2$ with (*S*,*S*,*S*)-bisdiazaphospholane (**12a**) resulted in 86% ee for the α-aldehyde (82% regioselectivity).[69] Nozaki et al. have achieved the AHF of a chiral 4-vinyl β-lactam using (*R*)-2-Nap-BIPNITE-*p*-F (**2**)[79] in an effort to develop a new synthetic route toward 1*β*-methylcarbapenem antibiotics.[80–84] Specialized approaches such as those employing directing groups[70,85–87] and catalytic amounts of scaffolding ligands[71,88–90] have been developed to control the regioselectivity of hydroformylation in organic synthesis. Tan and co-workers have developed a labile, chiral scaffolding ligand, **15**, containing a hemiaminal functional group, for the enantioselective hydroformylation of substituted allylamines (73–93% ee).[91,92] Zhang's group has recently reported the asymmetric hydroformylation of 1,1-disubstituted allylphthalimides to β^3-amino aldehydes in 55–95% ee's by using bisphospholane (*S*,*S*)-Ph-BPE (*ent*-**14**).[93]

The enantioselective hydroformylation of allyl alcohols, ethers, silyl ethers, and esters (**eq 5**) has been demonstrated with (*S*,*S*,*S*)-BisDiazaPhos **12a**[69] and (*R*,*S*)-YanPhos (**1d**)[78] following Nozaki's work using (*R*,*S*)-BinaPhos (**1a)** (not shown).[94] Allyl alcohol hydroformylation with **12a** yields predominantly (77%) the achiral linear aldehyde, while the branched aldehyde (23%) is obtained highly enantioselectively (95% ee).[69] Allyl silyl ethers and allyl phenyl ether undergo effective hydroformylation, yielding the α-aldehyde with excellent enantioselectivity (92–96% ee) and improved regioselectivity (64–72% α-aldehyde). Zhang's group disclosed that the hydroformylation of allyl phenyl ether and allyl acetate with **1d** leads to 94% ee of the branched α-aldehyde in both cases.[78] 1,3-alkoxy aldehydes and 1,3-silyloxy aldehydes (protected Roche aldehydes) are useful in polyketide total synthesis. Common methods for Roche aldehyde synthesis typically involve functional group manipulation of the Roche ester through protection, reduction to the primary alcohol, and oxidation to the aldehyde. In contrast, enantioselective hydroformylation using diazaphospholane ligands offers an alternative, scalable method for accessing Roche aldehydes from protected allyl alcohols (**Scheme 2**).[69,95] For example, rhodium-diazaphospholane catalysts enable 5,000 turnovers in the hydroformylation of allyl *tert*-butyldimethylsilyl ether on a gram scale (3.24−3.43 g) to give the desired aldehyde in 55–58% isolated yields.[95] The hydroformylation of TMS-protected Z-crotyl alcohol (α:β = 74:26, 94% ee) and cinnamyl alcohol (α:β <2:98, 90% ee) proceeds in reasonable 15- and 16-hour reaction times with (*S*,*S*,*S*)-BisDiazaPhos **12a**.[69]

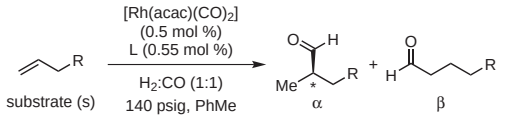
The enantioselective hydroformylation of α,β-unsaturated carbonyl substrates is not common because the branched dicarbonyl product can undergo rapid racemization via enolization. Faraone and co-workers reported the hydroformylation, in 95% conversion and 92% ee, of methyl acrylate to the branched aldehyde by using a (−)-menthol-derived phosphonite-pyridinyl bidentate ligand, **17** (**eq 6**, entry 1).[96] Clarke's group utilized (*S*,*S*,*S*)-bisdiazaphospholane **12a** in the AHF of *N*,*N*-dialkylacrylamides (not shown) and observed up to 82% ee.[97] Buchwald and Wang demonstrated the effective AHF of 1,1-disubstituted alkenes (α-alkylacrylates) to yield β-substituted aldehydes in 54–91% isolated yields and 81–94% ee's (eq 6, entries 2–4).[98] The α regioisomer was not observed in appreciable amounts in accordance with Keulemans' rule for 1,1-disubstituted alkenes.[99,100] Hydroformylation of α-alkylacrylates provides a synthetic route to 1,4-dicarbonyl structures that are present in pharmacologically active ingredients and biologically relevant molecules. Because the hydroformylation products of α,β-unsaturated carbonyls can undergo side reactions, protected analogues provide increased stability for the corresponding hydroformylation products. AHF with **12a** of acrolein derivatives protected as a 1,3-dioxolane (entry 5) or diacetoxy acetal (entry 7) yielded modest regio- (81% and 88% α:β ratio) and high enantioselectivities (92% and 93% ee, respectively).[69] Analogously,



R	R^1	R^2	α:β	ee[a]
b	*b*	H	98:2	95%
BnO	H	H	98:2	94%
t-BuO	H	H	97:3	99%
F_3C	H	H	98:2	99%
Me	H	Me	97:3	90%

[a] ee of the α isomer.
[b] $R,R^1 = C_6H_4$-1,2-$(CO)_2$.

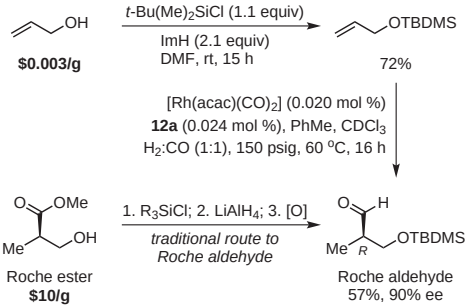
eq 4 *(Ref. 69)*



R	L	α:β	ee[a]	*Ref.*
HO	**12a**	23:77	95%	*69*
TMSO	**12a**	67:33	97%	*69*
TBSO	**12a**	67:33	96%	*69*
TBSO	**12a**	64:36	92%	*69*
PhO	**12a**	72:28	96%	*69*
PhO	*ent*-**1d**	71:29	94%	*78*
AcO	*ent*-**1d**	30:70	94%	*78*
b	**12a**	74:26	94%	*69*
c	**12a**	<2:98	90%	*69*

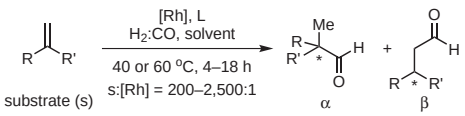
[a] ee of the α isomer. [b] Substrate = *cis*-$MeCH=CHCH_2OTMS$. [c] Substrate = *trans*-$PhCH=CHCH_2OH$.

eq 5



Scheme 2. AHF of Allyl Alcohol as an Alternative Route to Roche Aldehyde. *(Ref. 69,95)*

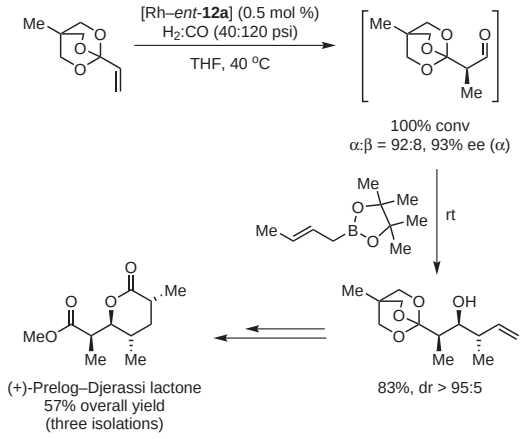
AHF of methyl vinyl ketone, protected as 2-methyl-2-vinyl-1,3-dioxolane, provided the α-aldehyde in 96% ee (entry 6). Burke and Risi employed *ent*-**12a** for the hydroformylation of a vinyl orthoester with improved regioselectivity (α:β = 92:8), while maintaining high enantioselectivity (93% ee). This same reaction was employed as the first step in the synthesis of the Prelog–Djerassi lactone (**Scheme 3**).[101] Leighton and co-workers have demonstrated the power of enantioselective hydroformylation in the total synthesis of dictyostatin.[102] Scalable syntheses of stereotriads C12−C14 and C20−C22 in fragments **A** and **B** (**Figure 4**) were accessed by hydroformylation of 2-vinyl-1,3-dioxolane and 2-methyl-2-vinyl-1,3-dioxolane at substrate:catalyst loadings of 6,667:1 and 3,333:1, respectively, and in the presence of rhodium-diazaphospholane catalyst *ent*-**12a** (**Scheme 4**).[102] One-pot, asymmetric, and Felkin-selective crotylation reactions of the branched aldehyde isolated from these hydroformylations yielded more than a gram of each of the stereotriads C12−C14 and C20−C22, using just 2 and 4 milligrams of ligand *ent*-**12a**! This unrivalled step-economical total synthesis of dictyostatin was achieved with a linear sequence of only 14 steps.



Entry	R	R'	L	α:β	ee[a]	*Ref.*
1	H	MeO_2C	**17**	97:3	92%	*96*
2	*i*-Pr	EtO_2C	**9**	only β	92%	*98*
3	Cy	EtO_2C	**9**	only β	94%	*98*
4	*c*-Pent	EtO_2C	**9**	only β	93%	*98*
5	H	$(H_2CO)_2CH$	**12a**	81:19	92%	*69*
6	H	$(H_2CO)_2CMe$	**12a**	70:30	96%	*69*
7	H	$(AcO)_2CH$	**12a**	88:12	93%	*69*
8	H	$MeC(H_2CO)_3C$	*ent*-**12a**	92:8	93%	*101*

[a] ee of the major isomer.

eq 6



Scheme 3. Application of the AHF of a Vinyl Orthoester in the Synthesis of Prelog–Djerassi Lactone. *(Ref. 101)*

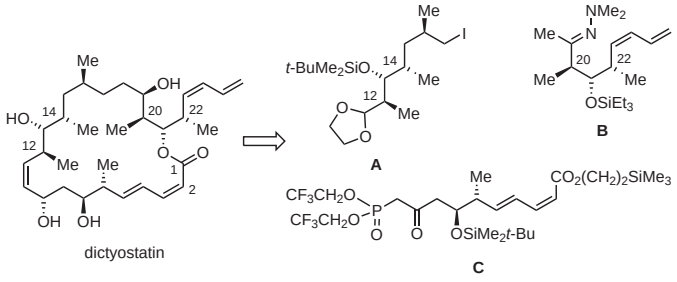
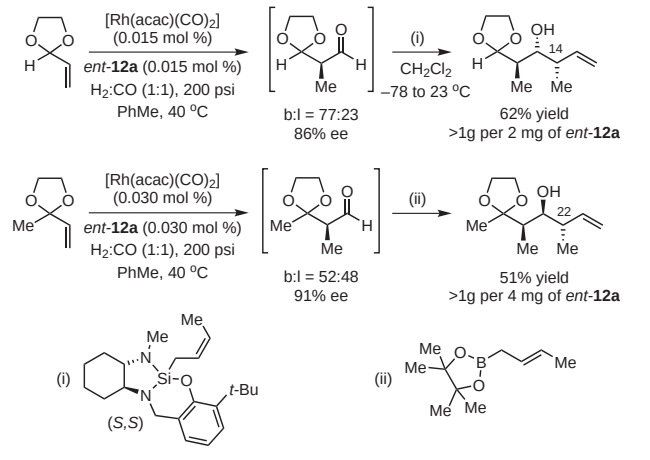


Figure 4. Leighton's Retrosynthetic Analysis of Dictyostatin. *(Ref. 102)*

2.4. Heterocycles

Chiral heterocycles such as pyrrolidines and tetrahydropyrans are common structural components of natural products. The asymmetric hydroformylation of 2,3-dihydropyrrole in the presence of (*R*,*S*)-BinaPhos (**1a**)[103] and (*S*,*S*,*S*)-BisdiazaPhos **12a**[69] gives 97% ee of the α-formyl product (a precursor of proline) in both cases (**eq 7**, entries 1 and 2). Conversely, the β-formyl isomer (a precursor of the β-amino acid) is accessible in 94% regioselectivity and 91% ee by hydroformylation of 2,5-dihydropyrrole with ligand **12a** (entry 3).[69] Reek and co-workers have effected the hydroformylation of 2,5-dihydrofuran using the phosphine–phosphite ligand **5** to give only the corresponding β-formyl regioisomer in 90% ee (entry 6).[104,105] Isomerization–hydroformylation of 2,3-dihydrofuran can be accomplished with ligand **5** to give the β-formyl aldehyde in high enantioselectivity (91% ee) but low conversion. In contrast, hydroformylation of 2,3-dihydrofuran using bisdiazaphospholane ligands *ent*-**12c** and *ent*-**12d** yields the α-formyl product in 78–79% regioselectivity and 90% ee (entries 4 and 5), while the 2,5-dihydrofuran preferentially gives the β-formyl product (entries 7 and 8; 97% regioselectivity and 95% ee for both ligands).[46] Burke and Clemens have reported the hydroformylation of *N*-Boc-2,2-dimethyl-3-oxazolidine to the synthetically useful Garner's aldehyde in high regio- (95%) and enantioselectivity (97%) using bisdiazaphospholane *ent*-**12a** (entry 9).[106]



Scheme 4. Leighton's Scalable, One-Pot, AHF Reactions in the Synthesis of the C12–C14 and C20–C22 Stereotriads of Dictyostatin. *(Ref. 102)*

2.5. 1,3-Dienes

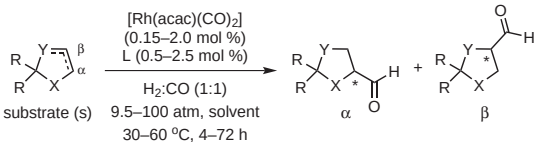
The hydroformylation of 1,3-dienes provides β,γ-unsaturated chiral aldehydes—key intermediates in polyketide synthesis. For example, Jacobsen and Lui have demonstrated the usefulness of the hydroformylation of 1,3-dienes [(*S*,*R*)-BinaPhos (*ent*-**1a**); b:l = 91:9, dr = 96:4] in setting the stereocenter at C15 in the total synthesis of (+)-ambruticin.[107] Similarly, Smith and co-workers have validated the use of (*R*,*S*)- and (*S*,*R*)-BinaPhos (**1a** and *ent*-**1a**) in the AHF of a diene intermediate in controlling the stereochemistry (dr > 95:5) at C10 of the C1–C12 fragment of tedanolide C.[108]

The hydroformylation of 1,3-butadienes can lead to 1-formyl, 2-formyl, and 4-formyl products, as well as products from alkene isomerization (**eq 8**). Hydroformylation of (*E*)-1-phenyl-1,3-butadiene, in the presence of (*R*,*S*)-BinaPhos (**1a**)[109] or (*S*,*S*,*S*)-bisdiazaphospholane (**12a**),[110] yields the 2-formyl product (**A**) (entries 1 and 2) in high regio- 92% and 99%) and enantioselectivities (90% and 91% ee). AHF of (*E*)-1-(2-furyl)-1,3-butadiene with **12a** enables the selective formation of the 2-formyl product (**A**) in 99% regioselectivity and 97% ee (entry 3). (*E*)-1-Methoxy- (entry 4), (*E*)-1-acetoxy- (entry 5), and (*E*)-1-triisopropylsilyloxy-1,3-butadienes (entry 6) all undergo effective AHF with high enantioselectivity [94%, 91%, and 90%, respectively, for the (*E*)-β,γ-unsaturated aldehyde]. Interestingly, hydroformylation of (*Z*)-1-triisopropylsilyloxy-1,3-butadiene (**Scheme 5**) results in the opposite absolute configuration of the aldehyde (70% ee) using the same enantiomer of the ligand (**12a**).[110] For this reason, stereochemically pure samples of (3*E*)-1,3-dienes are required to achieve highly enantioenriched aldehydes.

The enantioselective hydroformylation of (*E*)-1-carboethoxy-1,3-butadiene (eq 8, entry 7; 91% ee)[110] with **12a** offers a shorter synthetic route to the same aldehyde intermediate employed in the total synthesis of iejimalide B.[111] Fürstner and co-workers utilized six steps to synthesize a β,γ-unsaturated aldehyde from the Roche ester; the same intermediate can be accessed in one step through AHF of an achiral 1,3-diene. The hydroformylation, in the presence of **12b**, of 1-phenyl- and 1-(2-furanyl)-1,3-dienes, with methyl substitution at C2 (eq 8, entries 8 and 9), leads to the β,γ-unsaturated aldehyde in 88% and 98% regioselectivity, respectively, and 93% ee in both cases. 1-Vinylcyclohexene hydroformylation with ligands **1a** or **12b** affords the 2-formyl product (**A**) in an 86% and 88% ratio and in 96% and 92% ee, respectively (eq 8, entries 10 and 11). *Z*-selective hydroformylation was accomplished in the presence of an *E* alkene in the course of the hydroformylation of (1*E*,3*Z*)-1-phenyl-1,3-pentadiene with *ent*-**12a**, and resulted in the 2-formyl product (**A**) in 99% regioselectivity and 91% ee (entry 12).[110]

2.6. Other Alkenes

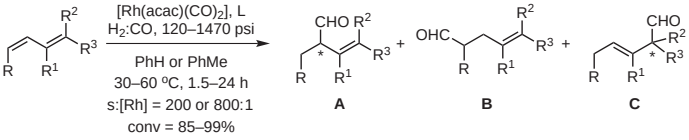
The industrial-scale hydroformylation of simple terminal alkenes, such as 1-hexene or 1-octene, has mainly aimed to optimize linear aldehyde formation. Reports of enantioselective hydroformylation of these substrates have been sparse, in part due to low selectivity for the branched aldehyde. Nozaki and co-workers have achieved the AHF of various aliphatic alkenes with (*R*,*S*)-BinaPhos (**1a**) and related ligands with varying levels of enantioselectivity (75–90% ee) and low-to-fair regioselectivity (8–30%).[44,112] Cobley, Clarke, and co-workers have utilized (S_{ax},*S*,*S*)-BobPhos (**6**) for the asymmetric hydroformylation of 1-hexene and other alkyl alkenes in up to 93% ee and 71–86%



X	Y	R	L	Conv	α:β	ee[a]	*R/S*	*Ref.*
NBoc	CH_2	H	**1a**	99%	67:33	97%	*S*	*103*
NBoc	CH_2	H	**12a**	99%	91:9	97%	----	*69*
NBoc	CH	H	**12a**	99%	6:94	91%	----	*69*
O	CH_2	H	*ent*-**12c**	45%	79:21	90%	*R*	*46*
O	CH_2	H	*ent*-**12d**	27%	78:22	90%	*R*	*46*
O	CH	H	**5**	97%	0:100	90%	*S*	*105*
O	CH	H	*ent*-**12c**	94%	<3:97	95%	*S*	*46*
O	CH	H	*ent*-**12d**	92%	<3:97	95%	*S*	*46*
NBoc	O	Me	*ent*-**12a**	70%[b]	95:5	97%	*S*	*106*

[a] ee of the major regioisomer. [b] Isolated yield.

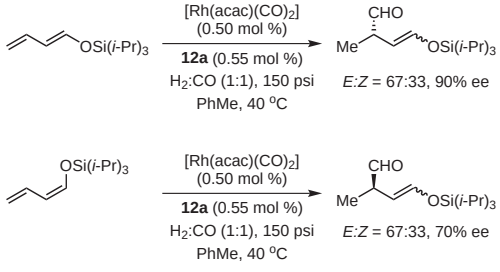
eq 7



Entry	R	R^1	R^2	R^3	**A**[a]	L	*E:Z*	*R/S*[b]	ee[b]	*Ref.*
1	H	H	H	Ph	92%	**1a**	----	*R*	90%	*109*
2	H	H	H	Ph	99%	**12a**	>99:1	*S*	91%	*110*
3	H	H	H	2-Fur	99%	**12a**	>99:1	*S*	97%	*110*
4	H	H	H	MeO	99%	**12a**	1:1	*S*	94%	*110*
5	H	H	H	AcO	60%	**12a**	1:1	*S*	91%	*110*
6	H	H	H	TIPSO	99%	**12a**	2.4:1	*S*	90%	*110*
7	H	H	Me	CO_2Et	95%	**12a**	>99:1	*S*	91%	*110*
8	H	Me	H	Ph	88%	**12b**	>99:1	*S*	93%	*110*
9	H	Me	H	2-Fur	98%	**12b**	>99:1	*S*	93%	*110*
10	H	*c*	H	*c*	86%	**1a**	----	*R*	96%	*109*
11	H	*c*	H	*c*	88%	**12b**	>99:1	*S*	92%	*110*
12	Me	H	H	Ph	99%	*ent*-**12a**	>99:1	*S*	91%	*110*

[a] Percent of isomer A in the product. [b] Configuration and ee of the *E* isomer. [c] R^1,R^3 = $(CH_2)_4$.

eq 8



Scheme 5. Opposite Stereochemical Outcomes in the AHF of the *E* and *Z* Isomers of 1-Tri(isopropyl)silyloxy-1,3-diene with the Same Enantiomer of Ligand **12a**. *(Ref. 110)*

regioselectivity at 16 °C.[113] Zhang's group has employed (*R,S*)-YanPhos (**1d**) in the hydroformylation of allyltrimethylsilane and allylbenzene both in 94% ee (72 and 42% regioselectivity).[78] Nozaki et al. have accomplished the hydroformylation of 3,3,3-trifluoropropene, with (*R,S*)-BinaPhos (**1a**), giving the α-aldehyde in 95% regioselectivity and 93% ee.[43] Huang, Bunel, and co-workers have effected the enantioselective rhodium-catalyzed hydroformylation of norbornenes in up to 93% ee in the presence of (*R,R,S,S*)-TangPhos (*ent*-**13a**).[114]

3. Conclusions and Outlook

The enantioselective *hydroformylation* of alkenes using rhodium-bisdiazaphospholane catalysts offers a practical method for the synthesis of functionalized chiral building blocks that approach the efficiency found in the catalytic, asymmetric *hydrogenation*. AHF of styrenes yields precursors to pharmacologically active, anti-inflammatory analgesics such as ibuprofen and naproxen. The protected α-hydroxy aldehydes resulting from the hydroformylation of vinyl esters have been employed in the synthesis of chiral isoxazolines and imidazoles, and in the synthesis of (+)-patulolide C. The hydroformylation of vinyl amides provides access to protected α-amino aldehydes. Protected allyl alcohol, acroleins, acrylates, and related analogues undergo AHF to synthetically useful precursors (e.g., Roche aldehydes) for natural product synthesis (e.g., Prelog–Djerassi lactone and dictyostatin). Exploiting the high activity and selectivity of robust rhodium-diazaphospholane catalysts enables scalable and practical syntheses of useful chiral building blocks for more complex products. The enantioselective hydroformylation of heterocycles yields useful aldehydes such as Garner's aldehyde or precursors to proline or β-proline. AHF of 1,3-dienes yields chiral β,γ-unsaturated aldehydes that are useful intermediates for natural product synthesis (e.g., (+)-ambruticin and tedanolide C). Simple alkyl alkenes remain a challenge in hydroformylation because of the difficulty in controlling the regioselectivity, but high levels of enantioselectivity have recently been achieved with several hybrid ligands.

Enantioselective hydroformylation is an emerging technology for the atom-efficient synthesis of chiral aldehydes. It is anticipated that new chiral ligands will offer solutions to present challenges in hydroformylation. In particular, the hydroformylation of disubstituted and trisubstituted alkenes would enable the synthesis of products with more diverse branching substituents. Reaction sequences that couple hydroformylation with hydrogenation, oxidation, olefination, hydroaminomethylation, etc., could capitalize on the inherent advantages of hydroformylation (gaseous reagents, essentially neutral conditions, fast rates, and large turnover numbers). Newer reactor technologies, such as flow reactors, could be applied to hydroformylation and would simplify the translation of bench-top reactions into scalable processes in the pharmaceutical environment. For the bench chemist, the replacement of synthesis gas with more easily handled equivalents; such as formalin, paraformaldehyde, or polyols; would make hydroformylation more attractive. These challenges and opportunities will continue to drive research into, and applications of, the enantioselective hydroformylation.

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5. References

(1) Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4301.
(2) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.
(3) Greenberg, W. A.; Varvak, A.; Hanson, S. R.; Wong, K.; Huang, H.; Chen, P.; Burk, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5788.
(4) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752.
(5) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152.
(6) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580.
(7) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.
(8) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.
(9) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.
(10) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.
(11) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.
(12) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233.
(13) Sonnet, P. E.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137.
(14) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(15) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.
(16) Davies, S. G.; Fletcher, A. M.; Thomson, J. E. *Chem. Commun.* **2013**, *49*, 8586.
(17) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796.
(18) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850.
(19) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305.
(20) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
(21) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.
(22) Noyori, R.; Kitamura, M.; Ohkuma, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5356.
(23) Nozaki, K.; Takaya, H.; Hiyama, T. *Top. Catal.* **1997**, *4*, 175.
(24) Van Leeuwen, P. W. N. M. In *Rhodium Catalyzed Hydroformylation*; van Leeuwen, P. W. N. M., Claver, C., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2000; Chapter 1, pp 1–13.
(25) Breit, B.; Seiche, W. *Synthesis* **2001**, 1.
(26) Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264.
(27) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113.
(28) Clarke, M. L. *Curr. Org. Chem.* **2005**, *9*, 701.
(29) Breit, B. Recent Advances in Alkene Hydroformylation. In *Metal Catalyzed Reductive C–C Bond Formation*; Krische, M. J., Ed.; Topics in Current Chemistry Series, Vol. 279; Springer: Berlin Heidelberg, Germany, 2007; pp 139–172.
(30) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251.
(31) Gual, A.; Godard, C.; Castillón, S.; Claver, C. *Tetrahedron: Asymmetry* **2010**, *21*, 1135.
(32) Franke, R.; Selent, D.; Börner, A. *Chem. Rev.* **2012**, *112*, 5675.
(33) Whiteker, G. T.; Cobley, C. J. Applications of Rhodium-Catalyzed Hydroformylation in the Pharmaceutical, Agrochemical, and Fragrance Industries. In *Organometallics as Catalysts in the Fine Chemical Industry*; Beller, M., Blaser, H.-U., Eds.; Topics in Organometallic Chemistry Series, Vol. 42; Springer: Berlin Heidelberg, Germany, 2012; pp 35–46.
(34) Chikkali, S. H.; van der Vlugt, J. I.; Reek, J. N. H. *Coord. Chem. Rev.*

2014, *262*, 1.
(35) Landis, C. R.; Jin, W.; Owen, J. S.; Clark, T. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3432.
(36) Landis, C. R.; Nelson, R. C.; Jin, W.; Bowman, A. C. *Organometallics* **2006**, *25*, 1377.
(37) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033.
(38) Brown, C. K.; Wilkinson, G. *Tetrahedron Lett.* **1969**, *10*, 1725.
(39) Brown, C. K.; Wilkinson, G. *J. Chem. Soc. A* **1970**, 2753.
(40) Van Leeuwen, P. W. N. M.; Roobeek, C. F. *J. Organomet. Chem.* **1983**, *258*, 343.
(41) Yan, Y.; Zhang, X. *J. Am. Chem. Soc.* **2006**, *128*, 7198.
(42) Higashizima, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron Lett.* **1994**, *35*, 2023.
(43) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413.
(44) Nozaki, K.; Matsuo, T.; Shibahara, F.; Hiyama, T. *Adv. Synth. Catal.* **2001**, *343*, 61.
(45) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040.
(46) Adint, T. T.; Wong, G. W.; Landis, C. R. *J. Org. Chem.* **2013**, *78*, 4231.
(47) Axtell, A. T.; Klosin, J.; Whiteker, G. T.; Cobley, C. J.; Fox, M. E.; Jackson, M.; Abboud, K. A. *Organometallics* **2009**, *28*, 2993.
(48) Zhang, X.; Cao, B.; Yan, Y.; Yu, S.; Ji, B.; Zhang, X. *Chem.—Eur. J.* **2010**, *16*, 871.
(49) Babin, J. E.; Whiteker, G. T. World Patent WO 93/03839, March 4, 1993.
(50) Babin, J. E.; Whiteker, G. T. U.S. Patent 5,360,938, November 1, 1994.
(51) Diéguez, M.; Pàmies, O.; Ruiz, A.; Castillón, S.; Claver, C. *Chem.—Eur. J.* **2001**, *7*, 3086.
(52) Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5834.
(53) Axtell, A. T.; Klosin, J.; Abboud, K. A. *Organometallics* **2006**, *25*, 5003.
(54) Noonan, G. M.; Cobley, C. J.; Mahoney, T.; Clarke, M. L. *Chem. Commun.* **2014**, *50*, 1475.
(55) Watkins, A. L.; Hashiguchi, B. G.; Landis, C. R. *Org. Lett.* **2008**, *10*, 4553.
(56) Watkins, A. L.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 10306.
(57) Nelsen, E. R.; Landis, C. R. *J. Am. Chem. Soc.* **2013**, *135*, 9636.
(58) Tonks, I. A.; Froese, R. D.; Landis, C. R. *ACS Catal.* **2013**, *3*, 2905.
(59) Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1994**, 395.
(60) Nakano, K.; Tanaka, R.; Nozaki, K. *Helv. Chim. Acta* **2006**, *89*, 1681.
(61) Tanaka, R.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2007**, *72*, 8671.
(62) Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R.; Abboud, K. A. *Org. Lett.* **2007**, *9*, 2665.
(63) Breeden, S.; Cole-Hamilton, D. J.; Foster, D. F.; Schwarz, G. J.; Wills, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4106.
(64) Zhao, B.; Peng, X.; Wang, Z.; Xia, C.; Ding, K. *Chem.—Eur. J.* **2008**, *14*, 7847.
(65) Mon, I.; Jose, D. A.; Vidal-Ferran, A. *Chem.—Eur. J.* **2013**, *19*, 2720.
(66) Wang, X.; Buchwald, S. L. *J. Org. Chem.* **2013**, *78*, 3429.
(67) Risi, R. M.; Burke, S. D. *Org. Lett.* **2012**, *14*, 1180.
(68) Wong, G. W.; Landis, C. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 1564.
(69) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027.
(70) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450.
(71) Tan, K. L. *ACS Catal.* **2011**, *1*, 877.
(72) Dydio, P.; Detz, R. J.; Reek, J. N. H. *J. Am. Chem. Soc.* **2013**, *135*, 10817.
(73) Lambers-Verstappen, M. M. H.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 478.
(74) Cobley, C. J.; Gardner, K.; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A.; Petersen, J. L.; Abboud, K. A. *J. Org. Chem.* **2004**, *69*, 4031.
(75) Simeone, J. P.; Bugianesi, R. L.; Ponpipom, M. M.; Goulet, M. T.; Levorse, M. S.; Desai, R. C. *Tetrahedron Lett.* **2001**, *42*, 6459.
(76) Ikeura, Y.; Ishimaru, T.; Doi, T.; Kawada, M.; Fujishima, A.; Natsugari, H. *Chem. Commun.* **1998**, 2141.
(77) Natsugari, H.; Ikeura, Y.; Kamo, I.; Ishimaru, T.; Ishichi, Y.; Fujishima, A.; Tanaka, T.; Kasahara, F.; Kawada, M.; Doi, T. *J. Med. Chem.* **1999**, *42*, 3982.
(78) Zhang, X.; Cao, B.; Yu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 4047.
(79) Nozaki, K.; Li, W.; Horiuchi, T.; Takaya, H.; Saito, T.; Yoshida, A.; Matsumura, K.; Kato, Y.; Imai, T.; Miura, T.; Kumobayashi, H. *J. Org. Chem.* **1996**, *61*, 7658.
(80) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.
(81) Shih, D. H.; Cama, L.; Christensen, B. G. *Tetrahedron Lett.* **1985**, *26*, 587.
(82) Shirai, F.; Nakai, T. *J. Org. Chem.* **1987**, *52*, 5491.
(83) Nagao, Y.; Nagase, Y.; Kumagai, T.; Matsunaga, H.; Abe, T.; Shimada, O.; Hayashi, T.; Inoue, Y. *J. Org. Chem.* **1992**, *57*, 4243.
(84) Tsukada, N.; Shimada, T.; Gyoung, Y. S.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 143.
(85) Breit, B.; Dauber, M.; Harms, K. *Chem.—Eur. J.* **1999**, *5*, 2819.
(86) Breit, B.; Breuninger, D. *J. Am. Chem. Soc.* **2004**, *126*, 10244.
(87) Breit, B.; Breuninger, D. *Eur. J. Org. Chem.* **2005**, *2005*, 3930.
(88) Sun, X.; Frimpong, K.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 11841.
(89) Lightburn, T. E.; De Paolis, O. A.; Cheng, K. H.; Tan, K. L. *Org. Lett.* **2011**, *13*, 2686.
(90) Yeung, C. S.; Dong, V. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 809.
(91) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757.
(92) Joe, C. L.; Tan, K. L. *J. Org. Chem.* **2011**, *76*, 7590.
(93) Zheng, X.; Cao, B.; Liu, T.; Zhang, X. *Adv. Synth. Catal.* **2013**, *355*, 679.
(94) Nozaki, K.; Li, W.; Horiuchi, T.; Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 4611.
(95) Wong, G. W.; Adint, T. T.; Landis, C. R. *Org. Synth.* **2012**, *89*, 243.
(96) Arena, C. G.; Nicolò, F.; Drommi, D.; Bruno, G.; Faraone, F. *J. Chem. Soc., Chem. Commun.* **1994**, 2251.
(97) Noonan, G. M.; Newton, D.; Cobley, C. J.; Suárez, A.; Pizzano, A.; Clarke, M. L. *Adv. Synth. Catal.* **2010**, *352*, 1047.
(98) Wang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 19080.
(99) Keulemans, A. I. M.; Kwantes, A.; van Bavel, T. *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 298.
(100) Uhlemann, M.; Börner, A. *ChemCatChem* **2012**, *4*, 753.
(101) Risi, R. M.; Burke, S. D. *Org. Lett.* **2012**, *14*, 2572.
(102) Ho, S.; Bucher, C.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 6757.
(103) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1997**, *62*, 4285.
(104) Chikkali, S. H.; Bellini, R.; Berthon-Gelloz, G.; van der Vlugt, J. I.; de Bruin, B.; Reek, J. N. H. *Chem. Commun.* **2010**, *46*, 1244.
(105) Chikkali, S. H.; Bellini, R.; de Bruin, B.; van der Vlugt, J. I.; Reek, J. N. H. *J. Am. Chem. Soc.* **2012**, *134*, 6607.
(106) Clemens, A. J. L.; Burke, S. D. *J. Org. Chem.* **2012**, *77*, 2983.
(107) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772.
(108) Smith, T. E.; Fink, S. J.; Levine, Z. G.; McClelland, K. A.; Zackheim, A. A.; Daub, M. E. *Org. Lett.* **2012**, *14*, 1452.
(109) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron* **1997**, *53*, 7795.
(110) Watkins, A. L.; Landis, C. R. *Org. Lett.* **2011**, *13*, 164.

(111) Fürstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Teplý, F.; Aïssa, C.; Moulin, E.; Müller, O. *J. Am. Chem. Soc.* **2007**, *129*, 9150.
(112) Nozaki, K.; Nanno, T.; Takaya, H. *J. Organomet. Chem.* **1997**, *527*, 103.
(113) Noonan, G. M.; Fuentes, J. A.; Cobley, C. J.; Clarke, M. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2477.
(114) Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P. J. *Tetrahedron Lett.* **2005**, *46*, 7831.

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Gene W. Wong received his undergraduate chemistry degree in 2007 from the University of Nevada, Reno, where he conducted undergraduate research with Professor Brian J. Frost on new water-soluble phosphine ligands. In 2012, he received his Ph.D. degree from the University of Wisconsin-Madison, working with Professor Clark R. Landis. His graduate studies focused on the synthesis of a library of bisdiazaphospholane ligands and their application in the rhodium-catalyzed asymmetric hydroformylation. Until his recent untimely death, Gene had been a research associate with Professor Karen I. Goldberg at the University of Washington.

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746398	Sodium chloride, anhydrous, free-flowing, Redi-Dri, ACS reagent, ≥99%
746371	Sodium iodide, anhydrous, free-flowing, Redi-Dri, ACS reagent, ≥99.5%
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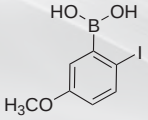
- Performs under ambient temperature
- Produces water as the sole byproduct



MIBA
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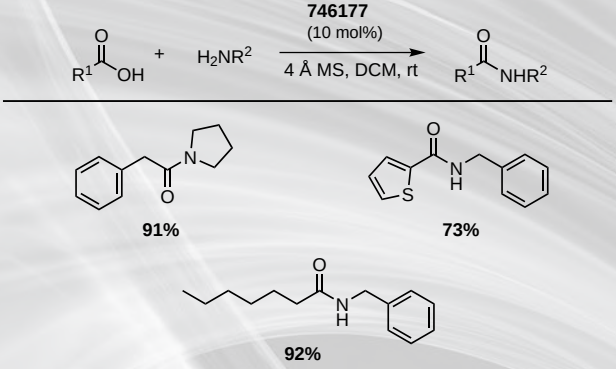

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References:
(1) Gernigon, N.; Al-Zoubi, R. M.; Hall, D. G. *J. Org. Chem.* **2012**, *77*, 8386.
(2) Al-Zoubi, R. M.; Hall, D. G. *Org. Lett.* **2010**, *12*, 2480.

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Boronic Acid Catalysis: an Atom-Economical Platform for Direct Activation and Functionalization of Carboxylic Acids and Alcohols

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Keywords. catalysis; boronic acids; atom-economy; green chemistry; direct amidation; Friedel–Crafts alkylation; cycloadditions; Meyer–Schuster rearrangement; allylic alcohol transposition.

Abstract. Boronic Acid Catalysis (BAC) offers an alternative strategy for activating hydroxyl-containing substrates such as carboxylic acids, alcohols, and other functional groups in a mild and selective manner. In the past five years alone, the list of reactions shown amenable to BAC has increased significantly. By avoiding the need for stoichiometric activation associated with the use of halide leaving groups and complex reagents, BAC provides better atom- and step-economy.

Outline

1. Introduction

Catalysis is ubiquitous to life and central to the chemical industry, where the discovery and development of sustainable processes rely heavily on advances in the field of catalysis. Indeed, catalysis, atom-economy, and reduction of derivatives constitute three of the *12 Principles of Green Chemistry*.[1] In this regard, the ACS Green Chemistry Institute Pharmaceutical Roundtable has identified a list of industrially relevant chemical reactions in need of greening, and fundamental transformations, such as amide formation from carboxylic acids and Friedel–Crafts alkylations, were ranked as top research priorities.[2] Over the past decade, catalysis of reactions by simple, metal-free organic compounds (organocatalysis) has also become an important area of research.[3] Compared with catalysts consisting of metal complexes, organocatalysts demonstrate many advantages including a lower sensitivity to moisture and oxygen, ease of preparation, low cost, and avoidance of drug regulatory issues for trace metals. Thus far, organocatalysis has been applied mainly to the activation of carbonyl-containing compounds (ketones, aldehydes) and imine derivatives.[3] Comparatively, very few strategies have been exploited for catalytically activating the hydroxyl group of carboxylic acids and alcohols via transient covalent-bond formation. A limited number of successful efforts to develop catalytic Mitsunobu-like and other reactions of secondary alcohols have been reported.[4] Strong Brønsted acids may be employed as catalysts and promoters of S_N1-type reactions of activated alcohols.[5] These conditions, however, often create issues of functional group incompatibilities. This review highlights an emerging, alternative strategy for activating hydroxyl-containing substrates such as carboxylic acids, alcohols, diols, and other functionalities in a mild and selective manner using boronic acids as catalysts.

2. Boronic Acid Catalysis (BAC)

Boronic acids are a particularly attractive class of synthetic intermediates because of their unique properties and reactivity as mild organic Lewis acids (sp^2-hybridized boron atom with a vacant orbital), combined with their stability and ease of handling.[6] Moreover, because of their low toxicity and their ultimate degradation into boric acid, boronic acids can be regarded as "green" (environmentally friendly) compounds. Most boronic acids exist as white crystalline solids, typically as mixtures of the free boronic acid together with its anhydride forms such as the 6-membered boroxine. Arylboronic acids, in particular, can be handled in air without special precautions, and most are chemically stable and display shelf-stability for long periods of time. Boronic acids can form covalent bonds with the hydroxyl groups of alcohols and carboxylic

acids in a reversible manner, providing a template upon which the reactants can be brought together and properly oriented in order to accelerate reactions (**Figure 1**). Faster reactions and unique selectivity are some of the main benefits provided by the synthetic strategy of "induced intramolecularity".[7]

The use of arylboronic acids as stoichiometric templates to enable chemical transformations has been demonstrated several decades ago. For instance, a boronic acid facilitated Diels–Alder cycloaddition was key to Nicolaou's total synthesis of Taxol® (**Scheme 1**, Part (a)),[8] and the Nagata hydroxyalkylation of phenols also requires boronic acids (Scheme 1, Part (b)).[9] The first reported use of boronic acids as reaction *catalysts* appears to date from 1963, when Letsinger and co-workers demonstrated that quinolin-8-ylboronic acid could promote the hydrolysis and alcoholysis of chlorine-substituted aliphatic alcohols in the presence of collidine to afford diols as the products (Scheme 1, Part (c)).[10] The boronic acid functionality serves as a template to hold the alcohol substrate through the formation of a covalent hemiester intermediate, and the nitrogen atom of the quinolin-8-ylboronic acid moiety assists chloride displacement presumably through a cooperative general base effect. Although this study had little practical value as a method to prepare glycols, it represents an important milestone for BAC as a type of organocatalysis.

Decades after Letsinger's seminal study, substituted arylboronic acids are emerging as a unique class of organocatalysts due to their Lewis acidity, which can be easily modulated by their substitution pattern (see Y in Figure 1, Part (a)).[11] Furthermore, *ortho*-substituted arylboronic acids can be regarded as bifunctional catalysts.[12] The boronic acid functionality can form temporary covalent bonds with alcohols, carboxylic acids, or amines that are readily cleaved in subsequent steps to allow catalytic recycling. These covalent intermediates can concomitantly activate the alcohol or carboxylic acid for a desired reaction. In this context, the *ortho*-substituent, X, can further activate the substrate, or serve as a handle or template for directing reagents via cooperative effects. The concept of BAC will be discussed and illustrated in the next sections with a review of the recent progress achieved with several different catalysts such as **1**–**12** (Figure 1, Part (b)).

3. Activation of Carboxylic Acids

Arylboronic acids react reversibly with carboxylic acids to generate a putative, monoacyl boronate species, which can provide electrophilic activation of the carboxylate group by an inductive effect that may be augmented through an intramolecular hydrogen bond. This mode of carboxyl activation has been successfully applied in several important organic reactions.

3.1. Direct Amidation of Carboxylic Acids

The first and most popular example of the boronic acid catalyzed activation of carboxylic acids is the preparation of amides. The amide bond is ubiquitous in naturally occurring compounds such as peptides and in synthetic commodity chemicals. In this respect, it has been reported that as much as 25% of all synthetic pharmaceutical drugs contain an amide unit.[13] A plethora of sophisticated and efficient methods

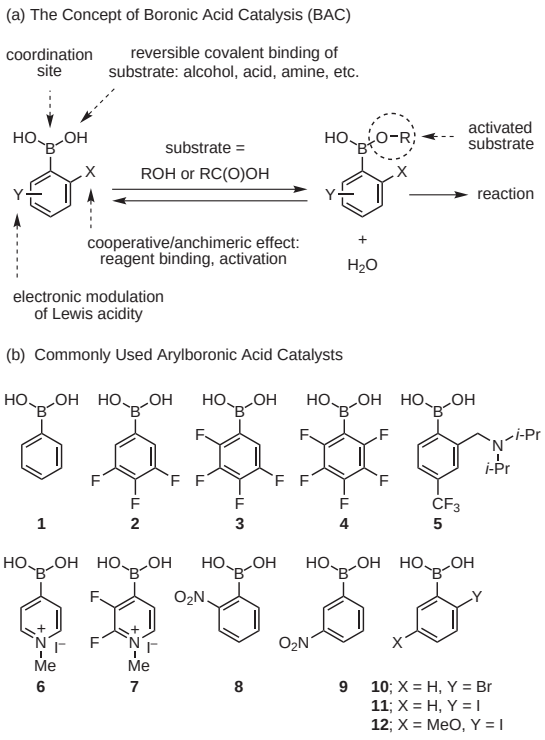
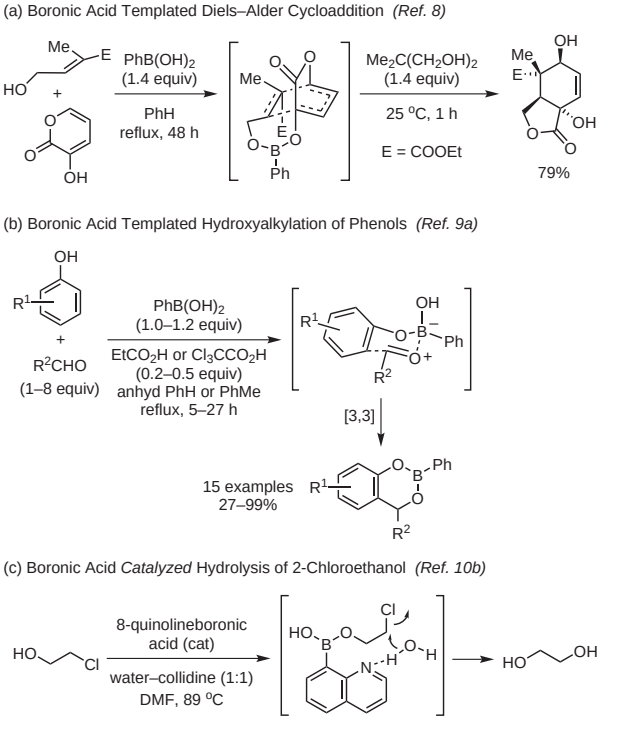


Figure 1. (a) Boronic Acid Catalysis, and (b) Common Arylboronic Acids Employed as Catalysts.



Scheme 1. Examples of Early Applications of Boronic Acids as Templates or Catalysts: (a) Diels–Alder Reaction, (b) Phenol Hydroxyalkylation, and (c) Boronic Acid Catalyzed Nucleophilic Hydrolysis.

employing dehydrating–activating reagents have been developed for the direct ("in situ") coupling of carboxylic acids and amines.[14] Common coupling reagents such as carbodiimides and phosphonium or uronium salts are expensive, often toxic, and provide poor atom-economy. These reagents and their associated co-reagents—including bases, supernucleophiles, and other additives—are required in stoichiometric excess and generate wasteful byproducts that complicate the isolation of the desired amide product. It is therefore not surprising that amide formation has been deemed the top-priority research area by the ACS Green Chemistry Institute Pharmaceutical Roundtable.[2] An ideal direct amidation reaction between carboxylic acids and amines would be a waste-free, catalytic, and operationally simple process occurring at ambient temperature. Despite the favorable thermodynamic stability of the resulting amide, the simple thermal dehydration between an amine and a carboxylic acid generally requires high temperatures, from 85 °C for some substrate combinations[15] to well over 150 °C for others.[16] These conditions may not be compatible with highly functionalized molecules, and this large energy barrier has made it very challenging to develop a direct amidation method between free carboxylic acids and amines at room temperature.[17]

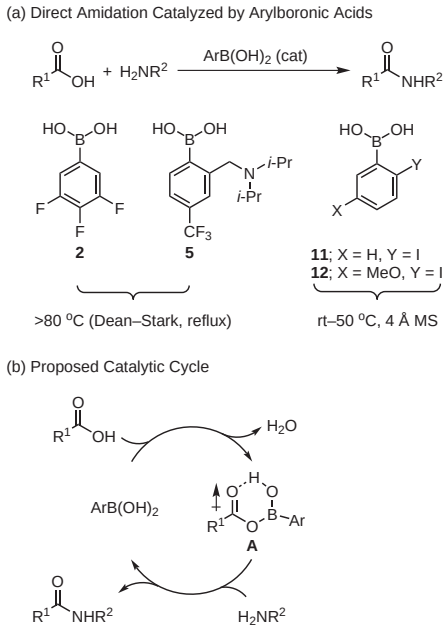
Boron compounds, used in a stoichiometric fashion, have long been known to promote direct amidation reactions.[18] In 1996, Yamamoto and co-workers described the first catalytic use of arylboronic acids for direct amidations,[19] and found electron-poor polyfluorinated arylboronic acids to be preferable. However, even the most efficient one, 3,4,5-trifluorophenylboronic acid (**2**), required reflux temperatures over 110 °C for several hours in nonpolar solvents. Other efficient arylboronic acids have been reported, such as Whiting's bifunctional 2-(diisopropylaminomethyl)-4-trifluoromethylphenylboronic acid (**5**)[20] and even boric acid.[21] All of these catalysts function at levated temperatures (**Scheme 2**, Part (a)). Following their initial discovery, Yamamoto and co-workers reported that the highly electron-deficient *N*-methyl-4-pyridiniumboronic acid (**6**, Figure 1) was more efficient than **2** in catalyzing direct amide formation,[22] and showed better thermal stability as compared to the 3-pyridinium isomer.[23] In both cases, the reaction needs to be realized under azeotropic reflux conditions (>110 °C). The superior catalytic activity of electron-deficient arylboronic acids is most likely the result of the enhanced Lewis acidity of the boron atom, which boosts the electrophilic activation of the carboxyl group in the proposed monoacyl boronate intermediate **A** (Scheme 2, Part (b)).

Soon after identifying catalyst **5**, Whiting and co-workers designed a chiral ferrocene-based bifunctional *ortho*-amino-substituted arylboronic acid for the kinetic asymmetric resolution of racemic α-substituted benzylamines with achiral carboxylic acids.[24] Although moderate yields and enantioselectivities (up to 41% ee) were obtained, this landmark study represented the first example of asymmetric direct amidation reactions, and opened up a new direction for the kinetic resolution of amines.

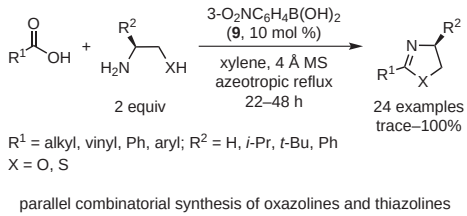
Wipf and Wang have exploited Yamamoto's direct amidation protocol in developing a method for the preparation of a combinatorial library of biologically active oxazolines and thiazolines (**eq 1**).[25] In this process, electron-deficient 3-nitrophenylboronic acid (**9**) was employed as catalyst to promote a tandem condensation–cyclodehydration of carboxylic acids with amino alcohols or amino thiols.[25]

In 2008, our group disclosed that *ortho*-iodophenylboronic acid (**11**) possesses superior catalytic activity for the direct amidation of carboxylic acids, and is effective at room temperature in the presence of molecular sieves.[26] Boronic acid **11** showed better catalytic efficiency than its analogues with a bromo or chloro substituent under the same reaction conditions. After carefully optimizing the arene core of the *ortho*-haloarylboronic acid with regards to the steric and electronic effects of ring substitution, 5-methoxy-2-iodophenylboronic acid (MIBA, **12**) was recently identified as the optimal new catalyst.[27] MIBA is kinetically more active than the parent, des-methoxy catalyst **11**, and provides higher yields of amide products in shorter reaction times under mild conditions at ambient temperature (**Scheme 3**).[26,27]

A thorough optimization of reaction conditions identified 4 Å molecular sieves as the optimal dehydrating agent, and methylene chloride, toluene, or 2-Me-THF as the optimal solvents with a substrate concentration of 0.07–0.1 M.[27] Because excess amine slows down the amidation, it is preferable to use a slight excess of the carboxylic acid. Moreover, the order of addition is critical. It is essential to premix the carboxylic acid and the catalyst in the presence of molecular sieves for several minutes prior to addition of the amine. All of the examples with the optimal MIBA catalyst (**12**) provided faster reactions and higher product yields when compared under identical conditions to the first-generation catalyst **11**.[27] The amidation reaction gives excellent yields within two hours at room temperature for most aliphatic substrates, and,

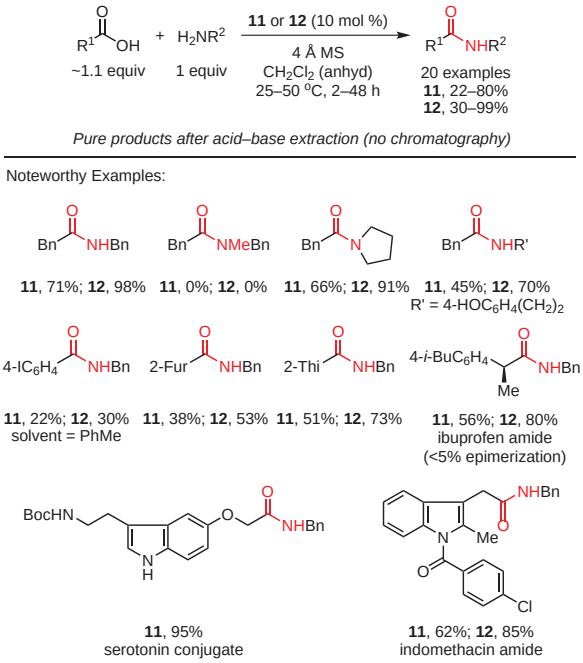


Scheme 2. The Boronic Acid Catalyzed Direct Amidation of Carboxylic Acids. *(Ref. 19,20,26,27)*



eq 1 *(Ref. 25)*

although an acyclic secondary amine failed to undergo the reaction, cyclic amines provided high yields of the desired amides. Aromatic amines (not shown) were unreactive, and aromatic carboxylic acids were found to require a higher reaction temperature to afford low yields after 48 hours. On the other hand, heteroaromatic carboxylic acids provided amide products in moderate-to-good yields in reactions performed at 50 °C. Highly functionalized substrates containing phenol, pyridine, and indole units were successfully employed to make biologically relevant amide products. One such amide that was prepared with ease using catalyst **12** is a derivative of the drug indomethacin known to inhibit COX-2 enzymes.[28] This method is in sharp contrast to a previously reported synthesis of the same amide that employs excess coupling reagents and a chromatographic purification.[28] The amidation of optically active (*S*)-ibuprofen with benzylamine led to the corresponding amide with less than 5% racemization. Given the propensity of ibuprofen and its amides to racemize,[29] this result demonstrates the mildness of these ambient conditions. These direct catalytic amidations are operationally simple, employ quasi-equimolar amounts of acid and amine, require no or low heating, and generate no byproducts. In many cases, pure amide products are isolated after a simple filtration and acid–base extractions to remove any unreacted substrates. It is noteworthy that, when the synthesis of BnCONHBn was repeated on a larger scale (5 mmol), the boronic acid catalyst was successfully recovered in high yield (90%) by simple acidification and extraction of the basic aqueous phase. When re-subjected to the same amidation reaction, the recovered catalyst afforded the same yield of product. Furthermore, our group has recently prepared a solid-supported prototype of the MIBA catalyst, and showed it to be competent in amidations of primary amines.[30]



Scheme 3. Direct Amidation Catalzyed by *ortho*-Iodoarylboronic Acids **11** and **12**. *(Ref. 26,27)*

3.2. Mechanistic Studies of the Boronic Acid Catalyzed Direct Amidation

The mechanism of the boronic acid catalyzed amidations, as proposed by Yamamoto and co-workers, was supported by the apparent observation of a monoacyl boronate intermediate (**A** in Scheme 2).[19] In our system, we ruled out the intermediacy of carboxylic acid anhydrides based on the observation that no acetic anhydride was observed when acetic acid and **11** were mixed alone under the direct amidation conditions.[26] Concerning the role of the ortho-iodide substituent, we established that the acidity of **11** is not abnormal (i.e, pK_a of 8.9 vs 8.8 for $PhB(OH)_2$)[26] and thus cannot explain its exceptional catalytic activity. Not only is the iodide substituent preferred, its ortho position is crucial. Indeed, both the para isomer and a naphthyl derivative are significantly less effective.[27] Other reaction variables play an intriguing role in this amidation reaction, and point towards a complicated reaction process. For instance, it was suggested that molecular sieves act both as a dehydrating agent and as a reversible reservoir of trace water. Although the detailed mechanism is uncertain at present, preliminary experiments by us suggest that the free boronic acid is the active catalyst (not the boroxine), and DFT calculations by Marcelli[31] suggest that the catalytic activity of *ortho*-haloarylboronic acids results from the Lewis basic character of the halogen atom. The latter would be implicated as an H-bond acceptor to facilitate the elimination of water from the orthoaminal intermediate proposed in the rate-determining step. Marcelli's DFT calculations imply the formation of an acylborate intermediate en route to the orthoaminal transition state (**TS**) shown in **Scheme 4**.[27,31] The catalyst accelerates the orthoaminal formation step (**A**•H_2O to **B**) by activating the acyl group for nucleophilic attack by the amine. Elimination of water from the orthoaminal intermediate (**B**), as depicted in the transition state (**TS**), becomes the rate-limiting step.[31] This step was proposed to be facilitated by a halogen–hydrogen bond that decreases the overall degrees of freedom while rendering the boron more electrophilic to ease the required shuffling of B–O bonds. In this scenario, compared to **11**, the optimal catalyst **12**, with a slightly more basic iodide, forms a stronger I···H bond that consequently leads to a lower activation energy. According to Marcelli's DFT calculations, the iodide substituent possesses the right size, geometry, and basicity to support the mechanism shown in Scheme 4.[31]

3.3. Esterification and Anhydride Formation

The electron-deficient *N*-methyl-4-pyridiniumboronic acid (**6**) catalyzes the esterification of hydroxycarboxylic acids with excess alcohols.[32] A hydroxyl group at the α or β position of the carboxylic acid is essential for the success of the reaction since it can participate in the formation of a tetrahedral acyloxyborate in the proposed intermediate.[32] A similar concept was recently applied to a dehydrative amidation of α-hydroxycarboxylic acids using alkylboronic acids as catalysts.[33] In light of the ability of Whiting's bifunctional *ortho*-aminomethyl-substituted arylboronic acid **5** to accelerate direct amidations, Ishihara and co-workers developed a similar bis(*ortho*-aminomethyl)-substituted arylboronic acid **13** to effectively catalyze the dehydrative intramolecular condensation of dicarboxylic acids to afford cyclic anhydrides at significantly milder temperatures as compared to the thermal variant (**eq 2**).[34] The authors claimed that boronic acid **13** works as a bifunctional catalyst, with the amine substituent serving as a Brønsted base to deprotonate the first carboxylic acid, thus increasing the nucleophilicity of the corresponding carboxylate functionality in the proposed monoacyl boronate intermediate.[34] Moreover, the second protonated amine substituent could act as a Brønsted acid to further activate the second (acceptor) carbonyl group through a relay of two hydrogen bonding interactions.

4. Activation of Unsaturated Carboxylic Acids

Because of the potential chemical incompatibility of the carboxylic acid group with other functional groups, the former is usually handled in a masked form, such as the ester, which in turn requires additional synthetic steps to prepare and remove. In this regard, a direct method for electrophilic (or LUMO-lowering) activation of unsaturated carboxylic acids towards cycloadditions would be very advantageous in terms of atom- and step-economy. Such a concept, employing boronic acids as catalysts, would mirror the strategy of iminium activation for unsaturated aldehydes and ketones.[3] We first demonstrated its application in [4 + 2] cycloadditions of acrylic acid with acyclic and cyclic 1,3-dienes catalyzed by arylboronic acids.[26]

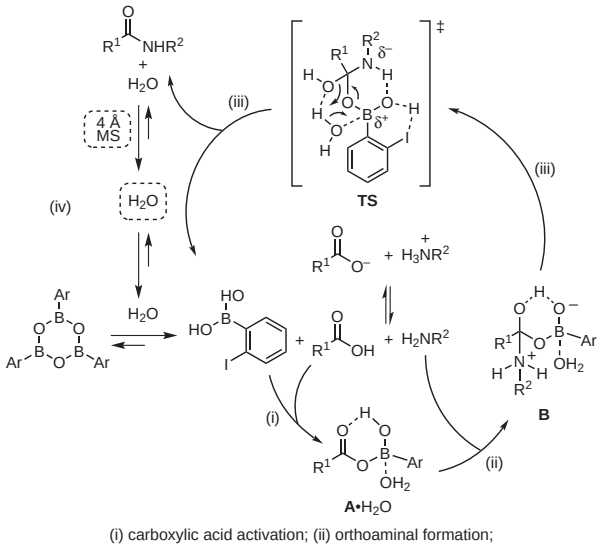
4.1. Diels–Alder Cycloadditions

Upon optimizing the boronic acid catalyzed [4 + 2] cycloaddition of acrylic acid and simple 1,3-dienes, it quickly became apparent to us that electron-poor boronic acids such as *ortho*-nitro- and *ortho*-bromophenylboronic acids **8** and **10** provide faster reaction rates (**Scheme 5**, Part (a)).[26,27] Moreover, the cycloaddition failed to proceed appreciably in the absence of catalyst, and there was no need for molecular sieves in these reactions (in fact, some water was required for catalyst turnover). This method was recently employed by Roussi and co-workers to prepare a complex bicyclic bridgehead carboxylic acid required in a biomimetic total synthesis of meiogynin A.[35] Alkynoic acids are suitable partners, and as with alkenoic acids, a remarkable increase in regioselectivity can be observed in the boronic acid catalyzed manifold (Scheme 5, Part (b)).[36]

4.2. Dipolar Cycloadditions: Huisgen Cycloaddition with Azides

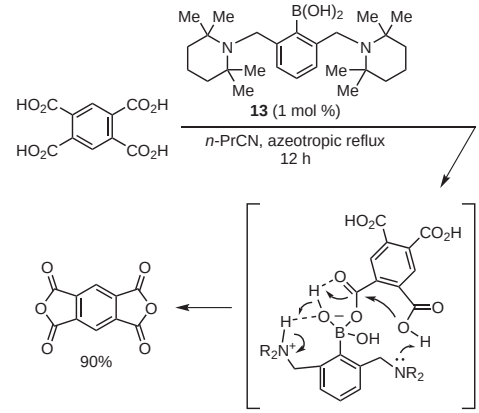
Our group extended the concept of BAC to the activation of unsaturated carboxylic acids in several classic dipolar [3 + 2] cycloadditions involving azides, nitrile oxides, and nitrones.[37] These cycloadditions produce pharmaceutically interesting small heterocyclic products such as triazoles, isoxazoles, and isoxazolidines. BAC allows these cycloadducts to be formed directly from the free carboxylic acid group (obviating the need for masking and unmasking the carboxylate through esterification steps), which can then be employed for further transformation. With optimal conditions in hand (2–20 mol % 2-$O_2NC_6H_4B(OH)_2$ (**8**) in $ClCH_2CH_2Cl$ at 25 °C), the scope of azide and alkyne substrates was examined for the Huisgen [3 + 2] cycloaddition (**Scheme 6**).[37] A wide variety of aliphatic and aromatic azides could be employed. Not only did the boronic acid catalyzed variant give greatly improved yields of 1,2,3-triazole products over the uncatalyzed reaction, but the regioselectivity was also significantly improved to the point of avoiding the need to separate regioisomers in most cases. Satisfactorily, it was found that 3-substituted 2-alkynoic acids can be successfully utilized provided a slightly elevated temperature or a longer reaction time is used. Alkenoic acids are not suitable substrates as indicated by the failure of acrylic acid to react with benzyl azide (not shown).

The boronic acid catalyzed Huisgen cycloaddition of acetylenic carboxylic acids does not only display an interesting substrate scope, it also circumvents the decarboxylation side reaction that plagues the thermal uncatalyzed variant.[38] For example, when run under typical conditions in refluxing 1,2-dichloroethane for just four hours,

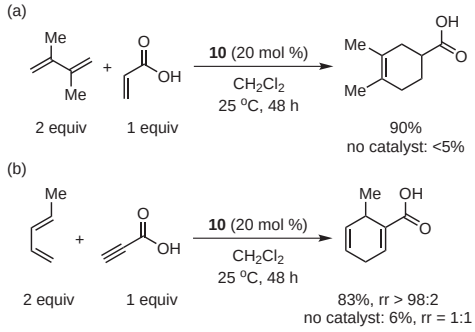


(i) carboxylic acid activation; (ii) orthoaminal formation; (iii) elimination of water from **B** is rate-limiting; (iv) dual role of molecular sieves as a reversible dehydrating agent.

Scheme 4. Proposed Catalytic Cycle for the Ambient, Direct Amidation Catalyzed by *ortho*-Iodoarylboronic Acids. *(Ref. 27,31)*



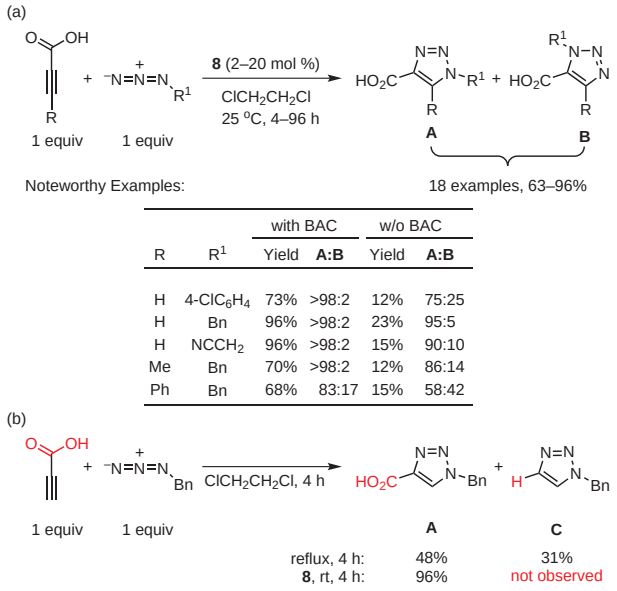
eq 2 *(Ref. 34)*



regioisomer ratio (rr) is for the 2-Me vs 3-Me product

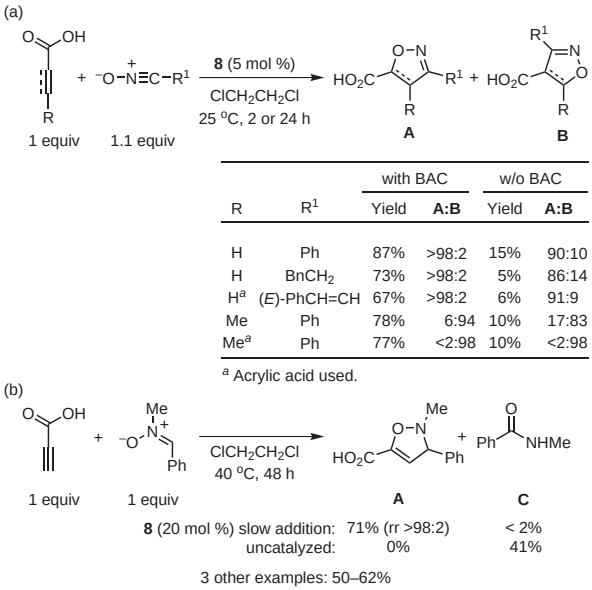
Scheme 5. Boronic Acid Catalyzed Diels–Alder Cycloadditions. *(Ref. 26,36)*

the product of cycloaddition of benzyl azide and propiolic acid was accompanied by as much as 31% of the corresponding decarboxylated adduct (Scheme 6, Part (b)). The BAC variant (**8**, rt, 4 h) completely suppressed this undesired pathway. This method was recently applied in the preparation of triazole-based prodrugs of novel acyclic nucleoside phosphonates.[39]



		with BAC		w/o BAC	
R	R^1	Yield	A:B	Yield	A:B
H	4-ClC_6H_4	73%	>98:2	12%	75:25
H	Bn	96%	>98:2	23%	95:5
H	$NCCH_2$	96%	>98:2	15%	90:10
Me	Bn	70%	>98:2	12%	86:14
Ph	Bn	68%	83:17	15%	58:42

Scheme 6. Boronic Acid Catalyzed Dipolar Cycloadditions between Alkynoic Acids and Azides to Produce 1,2,3-Triazoles. *(Ref. 37)*



		with BAC		w/o BAC	
R	R^1	Yield	A:B	Yield	A:B
H	Ph	87%	>98:2	15%	90:10
H	$BnCH_2$	73%	>98:2	5%	86:14
H[a]	(*E*)-PhCH=CH	67%	>98:2	6%	91:9
Me	Ph	78%	6:94	10%	17:83
Me[a]	Ph	77%	<2:98	10%	<2:98

[a] Acrylic acid used.

Scheme 7. Boronic Acid Catalyzed Dipolar Cycloadditions between Unsaturated Carboxylic Acids and Nitrile Oxides and Nitrones. *(Ref. 37)*

4.3. Cycloadditions with Nitrile Oxides and Other Dipoles

The generality of this activation concept was assessed in other types of [3 + 2] cycloadditions that afford valuable heterocyclic products. Remarkably, nitrile oxides and nitrones added to both alkynoic and alkenoic acids in the presence of 2-$O_2NC_6H_4B(OH)_2$ (**8**) as catalyst to give the corresponding isoxazoles and isoxazolines in much improved yields and regioselectivity when compared to the thermal, uncatalyzed reactions (**Scheme 7**, Part (a)).[37] Interestingly, in the cycloadditions of nitrile oxides, (unsubstituted) propiolic and acrylic acids tended to provide the sterically favored isomers, while 3-substituted alkynoic and alkenoic acids generated the opposite regioisomers as a result of electronic control. With nitrones, it was necessary to employ a special procedure to minimize the formation of the undesired amide, which can arise from the protic-acid-catalyzed Beckmann rearrangement of nitrones. Thus, the unsaturated carboxylic acid substrate was added slowly to the reaction mixture containing the catalyst so as to form the acylborate intermediate stoichiometrically, thus keeping the concentration of free carboxylic acid to a minimum (Scheme 7, Part (b)).

4.4. Mechanistic Studies of Boronic Acid Catalyzed Cycloadditions

Employing Childs's method,[40] we conducted NMR spectroscopic measurements whereby a large increase of 6.9 ppm was recorded for the ^{13}C NMR chemical shift of the β carbon (C3) of the monoacylated boronate of (*E*)-crotonic acid.[37] The extent of this chemical shift increase is comparable to the effect achieved in the complexation of methyl crotonate with moderate Lewis acids such as $SnCl_4$.[40] According to these results, 2-$O_2NC_6H_4B(OH)_2$ (**8**) catalyzes the cycloadditions through a powerful LUMO-lowering activation of the dienophile/dipolarophile by formation of a monoacylated covalent adduct **A** (see also Scheme 2) with the unsaturated carboxylic acid. Combined with the role of water in recycling the catalyst, this preliminary mechanistic study led to the catalytic cycle proposed in **Figure 2**.[37]

5. Activation of Alcohols

Arylboronic acids can provide electrophilic activation of the hydroxyl group of alcohols by facilitating the complete (or partial) ionization of the C–O bond to generate a carbocation intermediate. When applied to activated substrates such as allylic alcohols, regioselectivity becomes an issue as the reaction can proceed via two possible pathways depending on the degree of ionization of the C–O bond.

5.1. Friedel–Crafts Alkylations

In a landmark paper, McCubbin and co-workers reported that the highly Lewis acidic pentafluorophenylboronic acid (**4**) showed excellent catalytic activity in the regioselective Friedel–Crafts reaction of allylic alcohols at room temperature and in the presence of molecular sieves (**eq 3**).[41] When compared with other catalysts such as *p*-TsOH, BF_3, and $FeCl_3$, catalyst **4** provided a higher yield of product with one set of model substrates. However, only the most electron-rich arenes or heteroarenes are suitable substrates; for instance, even anisole is not reactive enough under these conditions. Nonetheless, a variety of highly substituted arenes and heteroarenes was prepared in this manner, and the Friedel–Crafts alkylation reaction was presumed to proceed through an S_N1' pathway involving an allylic carbocation with the regioselectivity being controlled by steric effects. Benzylic alcohols were also suitable substrates, but higher reaction temperatures were required (see eq 3, last example).[42] Later, the same group extended this catalytic system to propargylic alcohols, developing a highly effective and selective methodology for the propargylation and allenylation of electron-rich

aromatics.[43] Although the substrate scope is limited to highly electron-rich aromatic nucleophiles, these methodologies provide a milder and more environmentally friendly means for alcohol activation compared to existing strategies using Lewis acids, Brønsted acids, or transition-metal catalysts. Recently, our group identified improved Friedel–Crafts alkylation conditions by employing catalyst **7** (see structure in Figure 1) in nitromethane, which allowed less activated arenes to participate as substrates (**eq 4**).[44]

5.2. Intramolecular Trapping (Cyclization) of Alcohols

Our research group applied the BAC concept to the cyclization of allylic alcohols embedded with a pendent nucleophile.[45] Optimization studies identified catalysts that were notably superior to **4**, namely tetrafluorophenyl- and hexafluoronaphthylboronic acids, **3** and **14**, along with the most active catalyst, *N*-methyl-2,3-difluoropyridiniumboronic acid (**7**, Figure 1). Reaction optimization also identified nitromethane as the preferred solvent. Using these mild conditions at ambient temperature, or at 50 °C for the most difficult substrates, a variety of substrates were cyclized to provide carbocycles and heterocycles such as piperidines, pyrans, pyrrolidines, and tetrahydrofurans (**Scheme 8**).[45] It is notable that Brønsted acids, such as *p*-TsOH, provided much lower product yields, while BAC provided milder and cleaner reactions that are compatible with the use of acid-sensitive functional groups such as phenolic silyl ethers. Benzylic alcohols and tertiary alcohols are suitable substrates, although they require the most active catalyst **7** and a higher reaction temperature.

5.3. Nazarov Cyclization of Pentadienols

The Nazarov cyclization is a widely employed chemical transformation for the synthesis of substituted cyclopentenones. In its classical variant, a Lewis or Brønsted acid activates a divinyl ketone to generate a hydroxyl-substituted pentadienyl cation as a key intermediate, which then undergoes a 4π-electrocyclic ring closure to furnish the desired cyclopentenone product.[46] Although the Nazarov reaction of divinyl ketones has been studied extensively, there are only sporadic reports of divinyl alcohols being employed as starting materials.[47] Moreover, nearly all published methods require strongly acidic catalysts. We envisioned that a pentadienyl cation could be generated from divinyl alcohols under the mild conditions of boronic acid catalysis. This idea was validated when the resulting pentadienyl cations were shown to undergo the Nazarov cyclization to provide synthetically useful cyclic dienes by hydrogen elimination from the cyclopentenyl cations (**eq 5**).[48]

5.4. Transposition of Allylic and Propargylic Alcohols

The 1,3-transposition of allylic alcohols[49] and the related Meyer–Schuster rearrangement of propargylic alcohols[50] are synthetically useful processes. Although these isomerizations can be promoted in various ways, several methods require stoichiometric activation

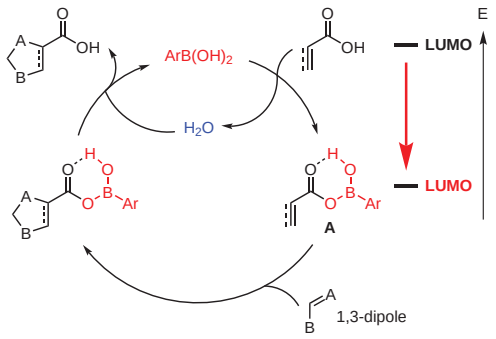
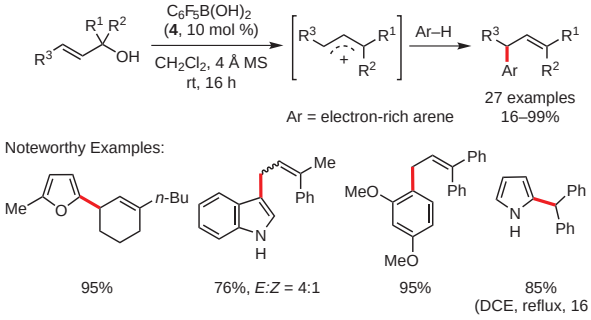
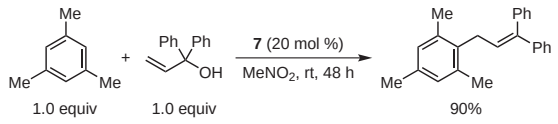


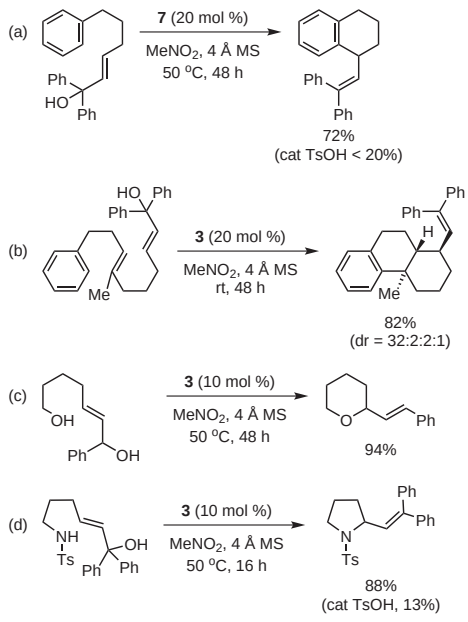
Figure 2. Proposed Mechanistic Cycle for the Boronic Acid Catalyzed Cycloadditions of Unsaturated Carboxylic Acids. *(Ref. 37)*



eq 3 *(Ref. 41,42)*



eq 4 *(Ref. 44)*



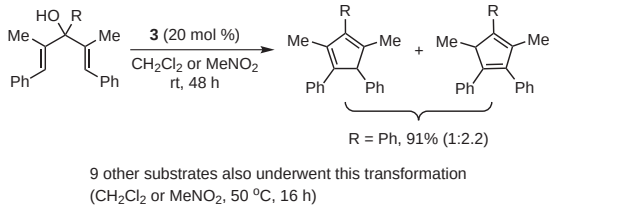
Scheme 8. Examples of Carbo- and Heterocyclizations of Allylic Alcohols Catalyzed by Boronic Acids. *(Ref. 45)*

of the hydroxyl group, while others employ transition metals or strong protic acid catalysts often under harsh conditions such as high temperatures.[49,50] Although rhenium(VII) oxo complexes are generally effective catalysts for allylic alcohols,[49] these complexes must be stored and used under strictly anhydrous conditions. Based on the mild Friedel–Crafts alkylations reported by McCubbin to take place by activation of allylic and benzylic alcohols with air-stable boronic acids,[41] we reasoned that allylic alcohols should rearrange selectively in the absence of an external nucleophile (**Scheme 9**).[51]

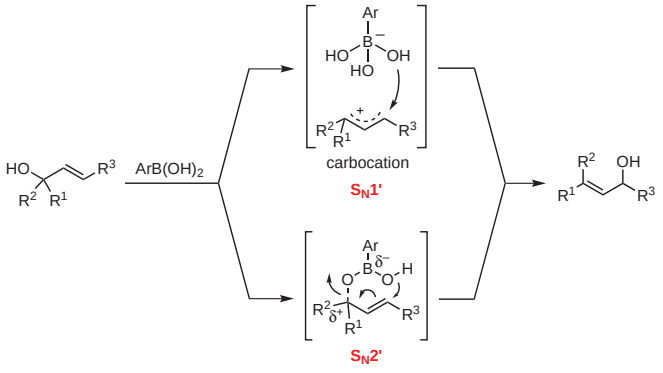
Reaction optimization, performed with 1-phenyl-2-propenol as a challenging model alcohol, revealed that highly electron-deficient polyfluorinated arylboronic acids are preferable.[51] Both 2,3,4,5-tetrafluorophenylboronic acid (**3**) and hexafluoronaphthylboronic acid (**14**) were significantly superior to pentafluorophenylboronic acid (**4**). Further optimization of solvent and catalyst loading confirmed that the use of 20 mol % of **3** or **14** in toluene provided the best reaction conditions. The use of molecular sieves was detrimental, while excess water suppressed the reaction. These observations suggest that a small quantity of water (formed by condensation between the boronic acid and the alcohol) is required for the catalytic turnover, but that a larger excess interferes with the formation of reactive intermediates. The substrate scope was explored using these optimal reactions conditions (**Scheme 10**).[51] Benzylic secondary and tertiary alcohols and tertiary non-benzylic alcohols were found to be suitable substrates. The transposition of allylic alcohols is potentially reversible, but it is driven forward in these examples by the formation of the thermodynamically favored alkene products incorporating a higher degree of substitution or extended conjugation. The less reactive allylic alcohols require catalyst **14** at elevated temperatures (50–80 °C). It is noteworthy that the *E*/*Z* selectivity of the boronic acid catalyzed reactions bettered that of the corresponding rhenium-catalyzed reactions (Scheme 10, Parts (b) and (c)).[52] For example, the isomerization of linalool into geraniol, an industrial process, proceeded with a selectivity superior to that of vanadium and rhenium oxo catalysts (Scheme 10, Part (c)).[52] Moreover, BAC succeeds where rhenium catalysis fails with functionalized substrates such as an Fmoc-protected piperidine (Scheme 10, Part (d)).[52] Substitution on the alkene unit was well tolerated except for strongly electron-withdrawing groups such as a carboxylic ester (examples not shown).

The corresponding transposition of propargylic alcohols, known as the Meyer–Schuster rearrangement, is a useful two-step alternative to phosphorus-based aldehyde olefination methods.[50] The facile addition of acetylide anions onto aldehydes and ketones provides the requisite propargylic alcohols, and BAC was very effective on those substrates too (Scheme 10, Parts (e) and (f)). Both terminal and disubstituted alkynes are suitable, including alkoxyacetylenes that afford the desired α,β-unsaturated esters in good yields and high *E*/*Z* selectivity (Scheme 10, Part (f)). If needed, thiophenol can be employed as an additive to promote in situ isomerization and afford higher *E*/*Z* selectivity. Unsaturated thioesters and amides were also prepared under similar conditions (not shown).[51] Phenylboronic acid can also be employed as a catalytic additive to help increase *E*/*Z* selectivity in the gold-catalyzed Meyer–Schuster reaction.[53]

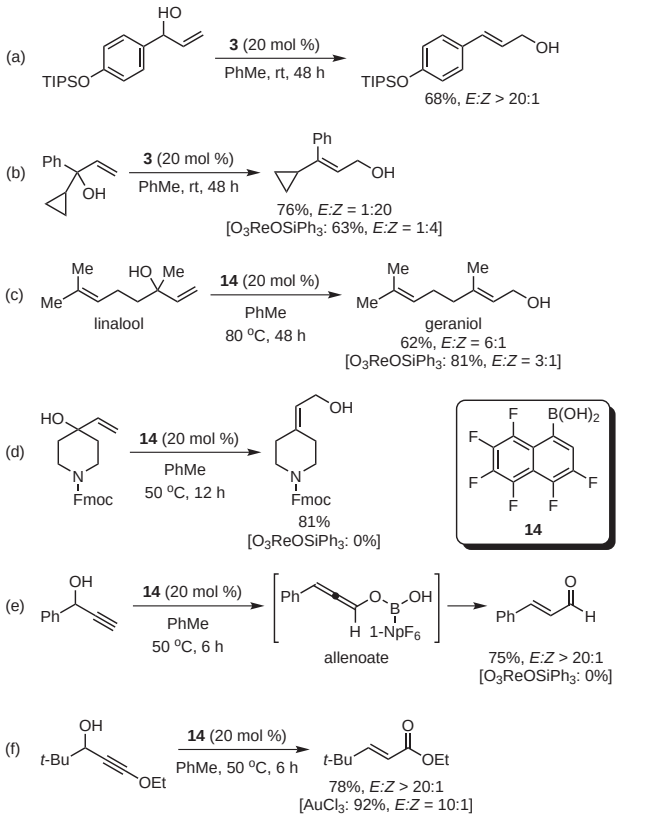
As demonstrated with this selection of substrates, it is worth noting that, in contrast to rhenium oxo and gold catalysis, BAC is effective



eq 5 *(Ref. 48)*



Scheme 9. Two Possible Mechanisms for the 1,3-Transposition of Allylic Alcohols. *(Ref. 51)*



Scheme 10. 1,3-Transposition of Allylic and Propargylic Alcohols. *(Ref. 51–53)*

with both allylic and propargylic alcohols, and it tolerates both acid- and base-sensitive groups. The boronic acid catalyst is robust under the reaction conditions, and is still fully effective even after 24 hours in the reaction mixture.[51] The scope of substrates, reaction times, and product yields of these 1,3-transpositions are suggestive of a polar mechanism involving partial or full ionization into an allylic (or propargylic) carbocation. Using O^{18}-labeled alcohol substrates, the reaction of a model propargylic alcohol was shown to proceed through an S_N1' mechanism (full ionization), whereas the reaction of a model allylic alcohol is likely to be more concerted (S_N2'-type) (see Scheme 9).[51]

5.5. Elimination and Cascade Reactions

In the course of our studies of the 1,3-transposition of allylic alcohols (see Section 5.4), our group demonstrated that the secondary aliphatic alcohol products from the 1,3-transposition of allylic alcohols can undergo a dehydrative elimination to give substituted butadienes when exposed to catalyst **3** (2,3,4,5-tetrafluorophenylboronic acid) for an extended period of time (**Scheme 11**).[51] This observation allowed the design of multicatalytic tandem reactions. For example, a substituted allylic alcohol can be subjected to a one-pot sequence of four reactions (1,3-transposition, elimination, [4 + 2] cycloaddition, and amidation) by employing three different boronic acid catalysts previously identified to be optimal for these respective reactions (see Scheme 11).[51]

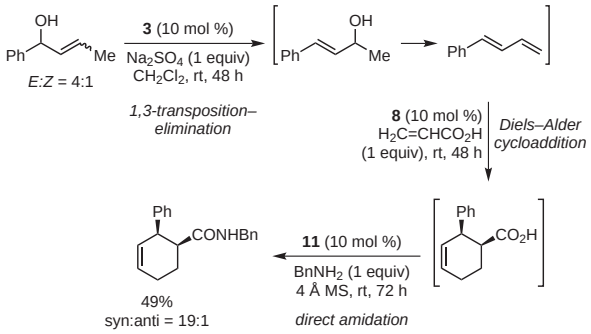
6. Activation of Carbonyl Groups

Because of their Lewis acidity, arylboronic acids can activate carbonyl compounds by increasing the electrophilicity of the carbonyl carbon or the nucleophilicity of the α carbon (i.e., via enolate formation) in a manner similar to that of other Lewis acids (**Figure 3**).[44] A number of interesting synthetic methodologies have been developed by employing this carbonyl activation concept.

In 2006, Debache and co-workers found that phenylboronic acid (**1**) can act as a catalyst to accelerate a one-pot, three-component (aromatic aldehydes, ethyl acetoacetate, and urea or thiourea) Biginelli reaction resulting in the synthesis of 3,4-dihydropyrimidinone derivatives (**Scheme 12**).[54] The authors proposed that the boronic acid was serving a dual function by increasing the nucleophilicity of ethyl acetoacetate through the formation of a boron enolate and enhancing the electrophilicity of the acylimine intermediate through boron–nitrogen coordination.[54] The same research group applied this concept to the preparation of 1,4-dihydropyridines and tetrahydrobenzo[*b*]pyrans.[55]

A number of similar methods for heterocycle synthesis catalyzed by phenylboronic acid (**1**) or 3-nitrophenyboronic acid (**9**) were reported by Bhusare and co-workers.[56] These authors proposed a mechanism involving the formation of a boron enolate; they also reported a related Mannich reaction that leads to β-amino carbonyl compounds.[57]

In 2008, Whiting and co-workers disclosed that *N*-butylbenzimidazole-2-phenylboronic acid sodium hydroxide complex (**15**) exhibits excellent catalytic activity for promoting the aldol addition and aldol condensation between hydroxyacetone or acetone and different aldehydes in water (**eq 6**).[58] Aldol addition products predominate with hydroxyacetone, whereas aldol condensation products are formed preferentially with acetone. The superior catalytic activity of **15** is believed to result from cooperative interactions from both the trihydroxyboronate unit and the imidazole function in the proposed transition state. When (*S*)-homoboroproline was employed as a chiral bifunctional catalyst in the aldol reaction between *para*-nitrobenzaldehyde and acetone, the *S* aldol product was obtained in 90% yield and 38% ee.[59] Interestingly, the tartrate boronic ester, formed in situ, provided an ee of 90%.



Scheme 11. Four-Reaction Synthetic Sequence Catalyzed by Three Different Boronic Acids. *(Ref. 51)*

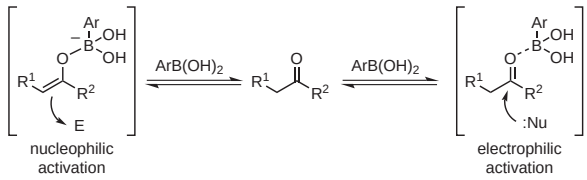
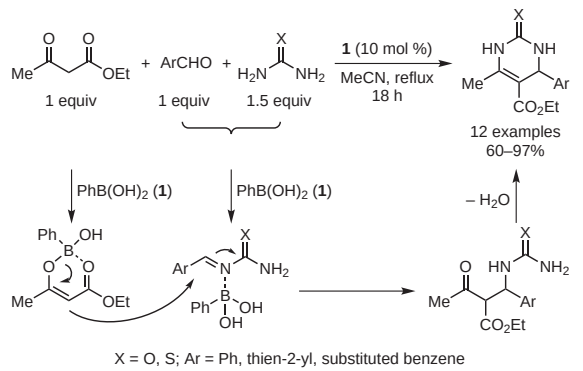
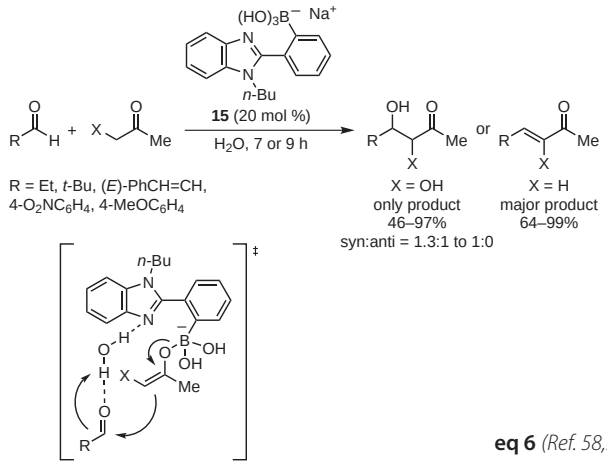


Figure 3. Activation of Carbonyl Groups with Arylboronic Acids. *(Ref. 44)*



Scheme 12. Biginelli Reaction Catalyzed by Phenylboronic Acid. *(Ref. 54)*



eq 6 *(Ref. 58,59)*

More recently, Dixon and co-workers utilized 3-nitrophenylboronic acid (**9**) to catalyze the enolization of 1,3-dicarbonyl compounds.[60] In refluxing toluene, the generated enol subsequently underwent a concerted ene carbocyclization with a pendent alkyne substituent to afford carbocyclic products in good yields. The reaction is reported to be efficient, easy to perform, and applies to a wide range of ketoester substrates.[60]

7. Other Reactions

In 1991, Rao and Philipp reported that phenylboronic acid (**1**) accelerates the hydrolysis rate of salicylaldehyde imines through a phenol-directed effect.[61] Bhusare and co-workers employed 3-chlorophenylboronic acid to promote imine formation and activation in the 3-aminoalkylation of indoles[62] and the cyclodensation of *ortho*-phenylenediamines with ketones.[63] Recently, Beller and co-workers developed a boronic acid catalyzed hydrosilylation of amides, which, in contrast to conventional amide reduction methods, required very mild reaction conditions and exhibited remarkable functional group tolerance.[64] Although these particular transformations have not yet been adopted by others, 3,4,5-trifluorophenylboronic acid (**2**) was reported to catalyze the reduction of carboxylic acids to alcohols with sodium borohydride,[65] and the direct formation of acylazides.[66] The same group reported the transesterification of β-keto esters catalyzed by 3-nitrophenylboronic acid (**9**).[67]

8. Conclusions and Outlook

This review has covered many contributions on Boronic Acid Catalysis (BAC) from our laboratory and from others. This promising emerging area of organocatalysis offers an alternative strategy for activating hydroxyl-containing substrates such as carboxylic acids, alcohols, and other functionalities in a mild and selective manner. In the past five years alone, the list of reactions amenable to BAC—which had comprised the amidation and esterification of carboxylic acids—has increased significantly to include [4 + 2] and dipolar cycloadditions of unsaturated carboxylic acids; Friedel–Crafts-type alkylations with alcohols; transpositions and eliminations of allylic alcohols; and reactions of carbonyl compounds such as aldol condensations, ene reaction, cyclocondensations, and others. Based on the current rate of discovery, we anticipate that many more reactions catalyzed by boronic acids are likely to be identified. With the proper improvements, such as more potent catalysts with higher turnover numbers, one can expect that BAC will be adopted by more chemists in search of methods that provide enhanced atom- and step-economy.

9. Acknowledgments

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10. References

(1) Anastas, P. T. *Green Chemistry: Theory and Practice*; Anastas, P. T., Warner, J. C., Eds.; Oxford University Press: New York, 1998, p 30.

(2) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.

(3) For recent reviews, see: (a) *Comprehensive Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2013. (b) Aleman, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774. (c) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406.

(4) (a) Kelly, B. D.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 13930. (b) Vanos, C. M.; Lambert, T. H. *Chem. Sci.* **2010**, *1*, 705. (c) Kelly, B. D.; Lambert, T. H. *Org. Lett.* **2011**, *13*, 740. (d) Vanos, C. M.; Lambert, T. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 12222. (e) Nacsa, E. D.; Lambert, T. H. *Org. Lett.* **2013**, *15*, 38. (f) Denton, R. M.; Jie, A.; Adeniran, B. *Chem. Commun.* **2010**, *46*, 3025. (g) Denton, R. M.; Jie, A.; Adeniran, B.; Blake, A. J.; Lewis, W.; Poulton, A. M. *J. Org. Chem.* **2011**, *76*, 6749. (h) Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nature Chem.* **2011**, *3*, 140. (i) Rueping, M.; Uria, U.; Lin, M.-Y.; Atodiresei, I. *J. Am. Chem. Soc.* **2011**, *133*, 3732. (j) Pronin, S. V.; Shenvi, R. A. *J. Am. Chem. Soc.* **2012**, *134*, 19604.

(5) (a) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501. (b) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, 647. (c) Baeza, A.; Nájera, C. *Synthesis* **2014**, *46*, 25.

(6) (a) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; Volumes 1 and 2. (b) Hall, D. G.; Zheng, H. Hydroxyboranes (Update 2011). In *Boron Compounds*. Science of Synthesis Knowledge Updates 2011/4; Hall, D. G., Ed.; Georg Thieme: Stuttgart, Germany, 2012; Volume 6, Section 6.1.7.11, pp 73–111.

(7) Tan, K. L. *ACS Catal.* **2011**, *1*, 877.

(8) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H. ; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634.

(9) (a) Nagata, W.; Okada, K.; Aoki, T. *Synthesis* **1979**, 365. (b) Murphy, W. S.; Tuladhar, S. M.; Duffy, B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 605. (c) Pettigrew, J. D.; Cadieux, J. A.; So, S. S. S.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 467.

(10) (a) Letsinger, R. L.; MacLean, D. B. *J. Am. Chem. Soc.* **1963**, *85*, 2230. (b) Letsinger, R. L.; Dandegaonker, S.; Vullo, W. J.; Morrison, J. D. *J. Am. Chem. Soc.* **1963**, *85*, 2223. (c) Letsinger, R. L.; Morrison, J. D. *J. Am. Chem. Soc.* **1963**, *85*, 2227.

(11) Dimitrijević, E.; Taylor, M. S. *ACS Catal.* **2013**, *3*, 945.

(12) (a) Georgiou, I.; Ilyashenko, G.; Whiting, A. *Acc. Chem. Res.* **2009**, *42*, 756. (b) Georgiou, I.; Whiting, A. Synthesis and Application of Aminoboronic Acids as Bifunctional Catalysts. Clean, Green, and Asymmetric! *Chimica Oggi–Chemistry Today* **2010**, *28* (3, May/June), pp IV–VI.

(13) (a) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55. (b) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.

(14) (a) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827. (b) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606.

(15) Arnold, K.; Davies, B.; Giles, R. L.; Grosjean, C.; Smith, G. E.; Whiting, A. *Adv. Synth. Catal.* **2006**, *348*, 813.

(16) (a) Charville, H.; Jackson, D.; Hodges, G.; Whiting, A. *Chem. Commun.* **2010**, *46*, 1813. (b) Charville, H.; Jackson, D. A.; Hodges, G.; Whiting, A.; Wilson, M. R. *Eur. J. Org. Chem.* **2011**, 5981.

(17) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471.

(18) (a) Nelson, P.; Pelter, A. *J. Chem. Soc.* **1965**, 5142. (b) Pelter, A.; Levitt, T. E.; Nelson, P. *Tetrahedron* **1970**, *26*, 1539. (c) Pelter, A.; Levitt, T. E. *Tetrahedron* **1970**, *26*, 1545. (d) Trapani, G.; Reho, A.; Latrofa, A. *Synthesis* **1983**, 1013. (e) Collum, D. B.; Chen, S.-C.; Ganem, B. *J. Org. Chem.* **1978**, *43*, 4393.

(19) (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196. (b) Maki, T.; Ishihara, K.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 8645.

(20) Arnold, K.; Batsanov, A. S.; Davies, B.; Whiting, A. *Green Chem.* **2008**, *10*, 124.
(21) (a) Tang, P. *Org. Synth.* **2005**, *81*, 262. (b) Mylavarapu, R. K.; Kondaiah, G. C. M.; Kolla, N.; Veeramalla, R.; Koilkonda, P.; Bhattacharya, A.; Bandichhor, R. *Org. Process Res. Dev.* **2007**, *11*, 1065. (c) Levonis, S. M.; Bornaghi, L. F.; Houston, T. A. *Aust. J. Chem.* **2007**, *60*, 821.
(22) Maki, Y.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 5043.
(23) Latta, R.; Springsteen, G.; Wang, B. *Synthesis* **2001**, 1611.
(24) Arnold, K.; Davies, B.; Herault, D.; Whiting, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2673.
(25) Wipf, P.; Wang, X. *J. Comb. Chem.* **2002**, *4*, 656.
(26) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 2876.
(27) Gernigon, N.; Al-Zoubi, R. M.; Hall, D. G. *J. Org. Chem.* **2012**, *77*, 8386.
(28) (a) Kalgutkar, A. S.; Marnett, A. B.; Crews, B. C.; Remmel, R. P.; Marnett, L. J. *J. Med. Chem.* **2000**, *43*, 2860. (b) Moth, C. W.; Prusakiewicz, J. J.; Marnett, L. J.; Lybrand, T. P. *J. Med. Chem.* **2005**, *48*, 3613.
(29) Yuchun, X.; Huizhou, L.; Jiayong, C. *Int. J. Pharm.* **2000**, *196*, 21.
(30) Gernigon, N.; Zheng, H.; Hall, D. G. *Tetrahedron Lett.* **2013**, *54*, 4475.
(31) Marcelli, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 6840.
(32) Maki,T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 5047.
(33) Yamashita, R.; Sakakura, A.; Ishihara, K. *Org. Lett.* **2013**, *15*, 3654.
(34) (a) Sakakura, A.; Ohkubo, T.; Yamashita, R.; Akakura, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 892. (b) Sakakura, A.; Yamashita, R.; Ohkubo, T.; Akakura, M.; Ishihara, K. *Aust. J. Chem.* **2011**, *64*, 1458.
(35) Fotsop, D. F.; Roussi, F.; Leverrier, A.; Bretéché, A.; Guéritte, F. *J. Org. Chem.* **2010**, *75*, 7412.
(36) Zheng, H.; Hall, D. G. *Tetrahedron Lett.* **2010**, *51*, 3561.
(37) Zheng, H.; McDonald, R.; Hall, D. G. *Chem.—Eur. J.* **2010**, *16*, 5454.
(38) (a) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; de Clercq, E.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185. (b) Salameh, B. A.; Leffler, H.; Nilsson, U. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3344.
(39) Hamada, M.; Roy, V.; McBrayer, T. R.; Whitaker, T.; Urbina-Blanco, C.; Nolan, S. P.; Balzarini, J.; Snoeck, R.; Andrei, G.; Schinazi, R. F.; Agrofoglio, L. A. *Eur. J. Med. Chem.* **2013**, *67*, 398.
(40) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801.
(41) McCubbin, J. A.; Hosseini, H.; Krokhin, O. V. *J. Org. Chem.* **2010**, *75*, 959.
(42) McCubbin, J. A.; Krokhin, O. V. *Tetrahedron Lett.* **2010**, *51*, 2447.
(43) McCubbin, J. A.; Nassar, C.; Krokhin, O. V. *Synthesis* **2011**, 3152.
(44) Zheng, H.; Hall, D. G. University of Alberta, Edmonton, AB, Canada. Unpublished work, 2012.
(45) Zheng, H.; Ghanbari, S.; Nakamura, S.; Hall, D. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 6187.
(46) (a) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (b) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (c) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (d) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 732.
(47) For recent examples, see: (a) Hastings, C. J.; Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 6938. (b) Narayan, R.; Fröhlich, R.; Würthwein, E.-U. *J. Org. Chem.* **2012**, *77*, 1868.
(48) Zheng, H.; Lejkowski, M.; Hall, D. G. *Tetrahedron Lett.* **2013**, *54*, 91.
(49) (a) Cadierno, V.; Crochet, P.; Gimeno, J. *Synlett* **2008**, 1105. (b) Ahlsten, N.; Bartoszewicz, A.; Martín-Matute, B. *Dalton Trans.* **2012**, *41*, 1660. (c) García-Álvarez, J.; García-Garrido, S. E.; Crochet, P.; Cadierno, V. *Curr. Top. Catal.* **2012**, *10*, 35.
(50) (a) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149. (b) Cadierno, V.; Crochet, P.; García-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2010**, *39*, 4015.
(51) Zheng, H.; Lejkowski, M.; Hall, D. G. *Chem. Sci.* **2011**, *2*, 1305.
(52) (a) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842. (b) Morrill, C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem.* **2006**, *71*, 7813.
(53) (a) Pennell, M. N.; Unthank, M. G.; Turner, P.; Sheppard, T. D. *J. Org. Chem.* **2011**, *76*, 1479. (b) Pennell, M. N.; Turner, P. G.; Sheppard, T. D. *Chem.—Eur. J.* **2012**, *18*, 4748.
(54) Debache, A.; Boumound, B.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Tetrahedron Lett.* **2006**, *47*, 5697.
(55) (a) Debache, A.; Boulcina, R.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Synlett* **2008**, 509. (b) Nemouchi, S.; Boulcina, R.; Carboni, B.; Debache, A. *Comptes Rendus Chimie* **2012**, *15*, 394.
(56) (a) Goswami, S. V.; Thorat, P. B.; Bhusare, S. R. *Heterocycl. Commun.* **2012**, *18*, 245. (b) Goswami, S. V.; Thorat, P. B.; Bhusare, S. R. *Tetrahedron Lett.* **2012**, *53*, 6771.
(57) Goswami, S. V.; Thorat, P. B.; Chakrawar, A. V.; Bhusare, S. R. *Mol. Divers.* **2013**, *17*, 33.
(58) Aelvoet, K.; Batsanov, A. S.; Blatch, A. J.; Grosjean, C.; Patrick, L. G. F.; Smethurst, C. A.; Whiting, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 768.
(59) (a) Arnold, K.; Batsanov, A. S.; Davies, B.; Grosjean, C.; Schütz, T.; Whiting, A.; Zawatzky, K. *Chem. Commun.* **2008**, 3879. (b) Georgiou, I.; Whiting, A. *Org. Biomol. Chem.* **2012**, *10*, 2422.
(60) Li, M.; Yang, T.; Dixon, D. J. *Chem. Commun.* **2010**, *46*, 2191.
(61) Rao, G.; Philipp, M. *J. Org. Chem.* **1991**, *56*, 1505.
(62) Goswami, S. V.; Thorat, P. B.; Kadam, V. N.; Khiste, S. A.; Bhusare, S. R. *Chin. Chem. Lett.* **2013**, *24*, 422.
(63) Goswami, S. V.; Thorat, P. B.; Bhusare, S. R. *J. Chem. Sci.* **2013**, *125*, 745.
(64) Li, Y.; Molina de La Torre, J. A.; Grabow, K.; Bentrup, U.; Junge, K.; Zhou, S.; Brückner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 11577.
(65) Tale, R. H.; Patil, K. M.; Dapurkar, S. E. *Tetrahedron Lett.* **2003**, *44*, 3427.
(66) Tale, R. H.; Patil, K. M. *Tetrahedron Lett.* **2002**, *43*, 9715.
(67) Tale, R. H.; Sagar, A. D.; Santan, H. D.; Adude, R. N. *Synlett* **2006**, 415.

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