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Highly Selective Rhodium-Catalyzed Conjugate Addition Reactions of 4-Oxobutenamides

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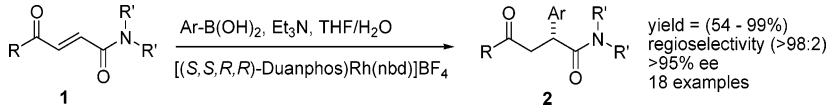

A variety of 4-oxobutenamides **1** were subjected to rhodium-catalyzed conjugate addition with arylboronic acids providing high regio- and enantioselectivity (97:3 to >99:1, >96% ee) and moderate to excellent yields (54−99%). The key to high selectivity is the use of sterically demanding *P*-chiral diphosphines, such as Tangphos or Duanphos. The product oxobutanamides **2** may be converted to alternate targets by selective derivatization of either the amide or ketone functional group. A stereochemical model predicting the absolute sense of induction was developed based on single-crystal X-ray structures of product and precatalyst.

First described in 1997, the addition of arylboronic acids to electron-deficient olefins catalyzed by rhodium(I) complexes has received considerable attention from the synthetic community as a powerful carbon−carbon bond-forming tool.[1] Shortly after their first report, Hayashi and Miyaura disclosed that the use of a chiral BINAP Rh(I) complex delivered superb enantioselectivities in the conjugate addition of arylboronic acids to simple unsaturated ketones.[2] The ligands[3] capable of delivering good enantiocontrol have expanded beyond the traditional chiral biaryl systems to chiral aminophosphites,[4] chiral diolefins,[5] and more recently phosphine−olefin based structures.[6] Further disclosures describe alternative electron-deficient olefins such as unsaturated esters,[7] amides,[8] nitroolefins,[9] phosphonates,[10] heteroaromatic alkenes,[11] symmetrical fumarates, and substituted and unsubstituted maleimides[12] as suitable electrophiles. Notably absent from the list are electronically differentiated 1,4-unsaturated dicarbonyl compounds[13] such as the oxobutenamides of type **1**.[14]

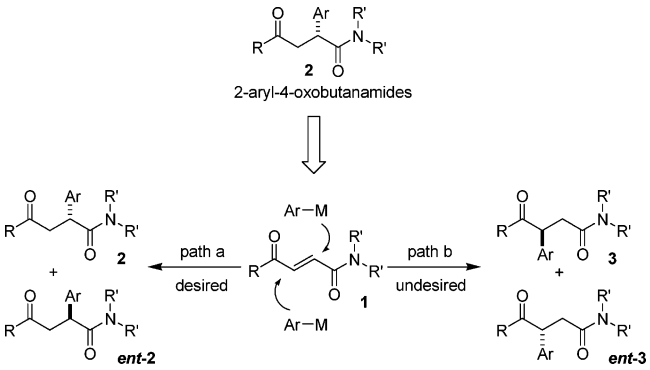

FIGURE 1. Regio- and enantiocontrol issues surrounding conjugate addition to 4-oxobutenamides.

(1) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16* (20), 4229−4231.

(2) Takaya, Y.; Ogasawra, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc*.**1998**, *120* (22), 5579−5580.

(3) (a) For an excellent review on the rhodium-catalyzed conjugate addition reaction see: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103* (8), 2829−2844. (b) For a review on rhodium-catalyzed C−C bond forming reactions see: Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103* (1), 169−196.

(4) (a) Boiteau, J.; Minnaard, A.; Feringa, B. *J. Org. Chem.* **2003**, *68* (24), 9481−9489. (b) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A.; Feringa, B. *Org. Lett.* **2003**, *5* (17), 3111−3113.

(5) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc*. **2003**, *125* (38), 11508−11509.

(6) Duan, W.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129* (7), 2130−2138.

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(8) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66* (26), 8944−8946.

(9) Hayashi, T.; Senda, T.; Ogasawra, M. *J. Am. Chem. Soc.* **2000**, *122* (43), 10716−10717.

(10) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawra, M. *J. Am. Chem. Soc*. **1999**, *121* (49), 11591−11512.

(11) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martin-Matute, B. *J. Am. Chem. Soc.* **2001**, *123* (22), 5358−5359.

(12) (a) Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6* (19), 3425−3427. (b) Shintani, R.; Duan, W.; Hayashi, T. *J. Am. Chem. Soc*. **2006**, *128* (17), 5628−5629. (c) Duan, W.; I, Y.; Shintani, R.; Hayashi, T. *Tetrahedron* **2007**, *63* (35), 8529−8536.

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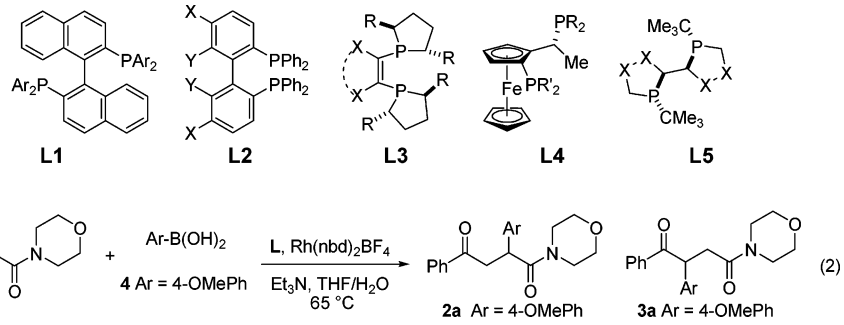
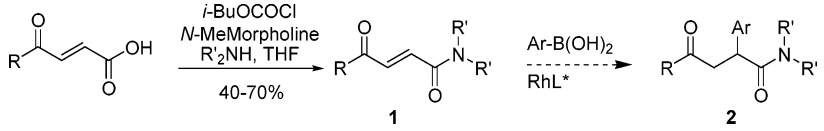


FIGURE 2. Ligand classes which were screened in the enantioselective conjugate addition reaction.

SCHEME 1. Proposed Route to 2-Aryl-4-oxobutanamides (eq 1)



Recently, we desired access to 2-aryl-4-oxobutanamides **2** in high enantiomeric purity. Routes to generate **2** with enantioselective transformations are limited and generally do not provide a direct approach to these structures.[15−17] We reasoned that a regio- and enantioselective conjugate addition to electrophile **1** would allow direct and flexible access to **2**. Oxobutenamides of type **1** (R = Ph, Me) are easily prepared from commercially available acylacrylic acids (Scheme 1).[18] The use of oxobutenamides as electrophilic coupling partners, however, presents a particularly daunting challenge; the transformation needs to be highly enantio- and regioselective requiring a catalyst system that distinguishes not only enantiotopic π-faces but also the subtle electronic differences of each conjugate acceptor (Figure 1).[19]

Initially studying **1a**, we examined a variety of commercially available phosphorus-based ligands **L1**−**L5** (Figure 2).[20] The commonly utilized chiral biaryl ligands of type **L1** and **L2** provided good enantioselecitivities ranging from 85% to 92%, but only moderate regioselectivities (~9:1) favoring the desired 2-aryl-4-oxobutanamides **2**. More electron donating ligands, such as the chiral phospholanes **L3**, afforded almost exclusively the desired regioisomer (>98:2; **2**:**3**), although the enantioselectivities were lower (0−61% ee) than those with the biaryl ligand systems. Ligands of class **L4** failed to show significant reactivity (conversions <20%). Sterically demanding *P*-chiral phosphines **L5,** e.g. Tangphos[21] and Duanphos,[22] afforded excellent enantioselectivity while still maintaining high regioselectivity, delivering the desired regioisomer in >99:1 (**2**:**3**) and 95−98% ee. To our knowledge, this is the first instance where these *P*-chiral phosphines have been utilized in an enantioselective conjugate addition reaction.[23] While the unbound phosphine is rapidly oxidized in air, the bench-stable complex [((*S*,*S*,*R*,*R*)-Duanphos)Rh(nbd)]BF_4 **5**[24] afforded identical results to those of the in situ prepared precatalyst and was used in further studies.[25]

A screen of reaction conditions in the conjugate addition of **1a** with **4** mediated by catalyst **5** established that the reaction was tolerant of a number of ethereal solvents and mild bases. Potassium carbonate, potassium bicarbonate, potassium hydroxide, triethylamine, and diisopropylethylamine all afforded full conversion to the desired product with no appreciable difference in selectivity and with no specific advantage over triethylamine. The use of potassium acetate, however, resulted in low conversion (<50%). With a base selected, solvent effects were next examined. Tetrahydrofuran, 2-methyltetrahydrofuran, and 1,4-dioxane were preferred over 1,2-dimethoxyethane, which afforded lower enantioselectivity (90% ee). Alcoholic solvents such as methanol, ethanol, and 2-propanol afforded 1,4-conjugate reduction of the enone with little or no nucleophilic addition taking place. The optimized conditions described in eq 2[26] were used for further reaction characterization. While catalyst loading was not fully explored, we found that a 2 mol % catalyst loading was sufficient for the majority of substrates studied. On a 12 mmol scale, the reaction was complete in 6 h at 65 °C (100% conversion; >99:1 regioselectivity, 98% ee; eq 3). HPLC analysis of the crude reaction mixture calibrated with an external standard showed a 93% solution assay for the

(13) Recently, Hoveyda has reported a regio- and enantioselective copper-catalyzed conjugate addition of organozinc reagents to cyclic γ-ketoesters: Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46* (7), 1097−1100.

(14) For a recent report on the preparation of oxobutenamides: Sonye, J. P.; Koide, K. *J. Org. Chem.* **2006**, *71* (16), 6254−6257.

(15) Hoffman, R. V.; Kim, H. W. *Tetrahedron Lett.* **1993**, *34* (13), 2051−2054.

(16) Hayashi, T.; Yamamoto, A.; Ito, Y. *Chem. Lett.* **1987**, *1*, 177−180.

(17) For a complementary approach that provides α-aryl ketoamides of type **3** with moderate to high enantioselectivity see: Nahm, M. R.; Xin, L.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2005**, *44* (16), 2377−2379.

(18) Lawrence, D. S.; Zilfou, J. T.; Smith, C. D. *J. Med. Chem.* **1999**, *42* (24), 4932−4941.

(19) (a) Captain, L. F.; Xia, X.; Liotta, D. C. *Tetrahedron Lett.* **1996**, *37* (25), 4293−4296. (b) Stack, J. G.; Curran, D. P.; Rebek, J.; Ballaster, P. *J. Am. Chem. Soc.* **1991**, *113* (15), 5918−5920.

(20) For a complete table of ligands screened and the results, see the Supporting Information

(21) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612−1614.

(22) (a) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, *4*, 646−649. (b) Liu, D.; Gao, W.; Wang, C.; Zhang, X. *Angew. Chem., Int. Ed.* **2005**, *44* (11), 646−649.

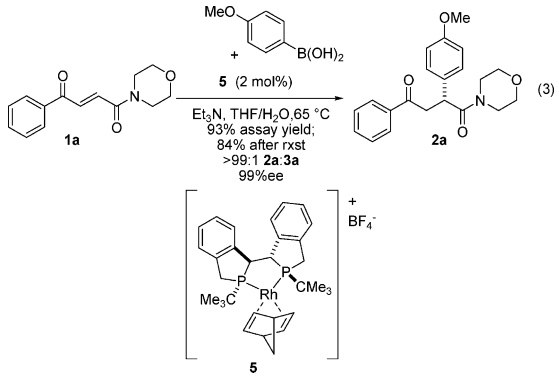
(23) While specifically Tangphos and Duanphos have not to our knowledge been used in the rhodium-catalyzed 1,4-conjugate addition reaction, P-Chiral phosphines have demonstrated high enantioselectivity in the conjugate addition reaction to cyclic and acyclic enones: Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127* (34), 11934−11935.

(24) nbd = bicyclo[2.2.1]hepta-2,5-diene.

(25) Both enantiomers of the Duanphos ligand as well as the corresponding LRh(cod)BF_4 complexes may be obtained from Chiralquest Inc. or alternatively the R,R,S,S-antipode of both ligand and Rh(cod)BF_4 complex is sold by Strem chemicals.

(26) Reagents and conditions: 2 mol % of **5**, 1.5 equiv of **4**, 1.5 equiv of Et_3N, 19:1 THF:H_2O, 65 °C.

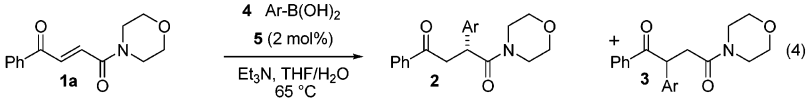
desired product **2a**. A simple aqueous workup, followed by recrystallization of the desired product from heptane:isopropanol (4:1) afforded **2a** in 84% isolated yield,[27] >99% regioselectivity, 99% ee.

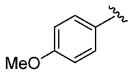
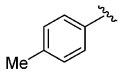
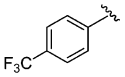
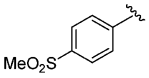
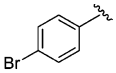
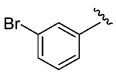
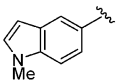
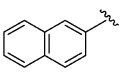
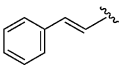


With an appropriate set of reaction conditions, the generality of the regioselective conjugate addition with respect to the nucleophillic coupling partner was examined (Table 1). A wide variety of commercially available meta- and para-substituted boronic acids were found to be competent coupling partners with **1a** (Table 1). Both electron rich (**4a**,**b**) and electron poor (**4d**,**e**) boronic acids afforded high enantio- and regioselectivity mediated by complex **5**. The indolyl boronic acid **4g** afforded the conjugate addition product **2g** in excellent enantioselectivity, albeit with slightly diminished regioselectivity (Table 1, entry 7). (*E*)-Styrylboronic acid is also an efficient nucleophile in this reaction manifold, affording the conjugate addition product **2i** in 92% yield and essentially a single isomer (Table 1, entry 9). The absolute configuration of **2e** and **2f** was determined to be *R* by single-crystal X-ray structure analysis, and the configurations of the remaining addition products were assigned by analogy.

The conjugate addition reaction to **1a** mediated by complex **5** was also tolerant of ortho substitution on the boronic acid nucleophile, and excellent regioselectivities and enantioselectivities were obtained in the majority of cases (Table 2). With

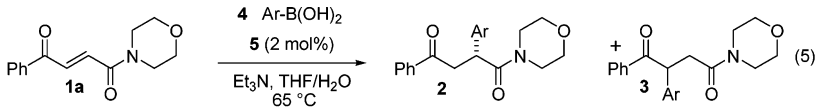
TABLE 1. Effect of Boronic Acid Structure on Yield, Product Distribution, and Enantioselectivity in the Reaction of 1a (eq 4)[a]

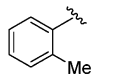
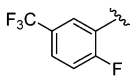


Entry	Ar =	Product[f]	2:3[b]	Yield[d]	%ee 2[c]
1		**2a**	>99:1	93	98
2		**2b**	>99:1	99	98
3		**2c**	>99:1	97	>99
4		**2d**	>99:1	98	98
5		**2e**[e]	99:1	73	99
6		**2f**[e]	>99:1	99	93
7		**2g**	90:10	71	97
8		**2h**	99:1	60	98
9		**2i**	>99:1	92	99

[a] Reactions were conducted at 65 °C for 24 h, using 1.5 equiv of **4**, 1.5 equiv of Et_3N, 2 mol % of **5** in THF:H_2O 19:1 (10 mL/g of **1a**). [b] As measured by HPLC: peak area percent **2**:**3**. [c] Determined by chiral HPLC analysis of major regioisomer **2** (see the Supporting Information). [d] Isolated yield based upon the average of two separate reactions. [e] Absolute configuration determined by single-crystal X-ray diffraction (see the Supporting Information). [f] Product configuration assigned for **2e** and **2f**. All others assigned by analogy.

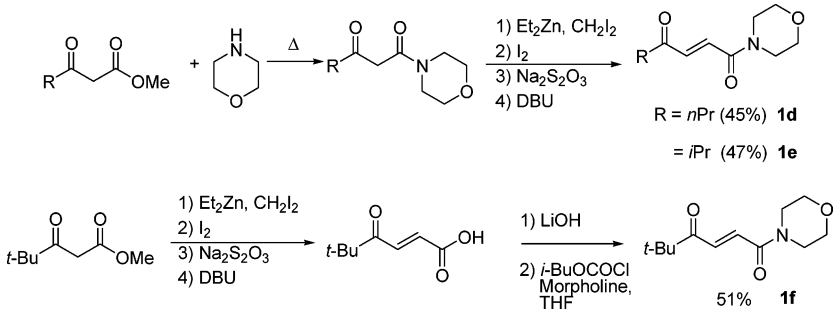
TABLE 2. Effect of Boronic Acid Structure on Yield, Product Distribution, and Enantioselectivity in the Reaction of 1 (eq 5)[a]



Entry	Ar =	Product[e]	2:3[b]	Yield[d]	%ee[c]
1		**2j**	>99:1	99	>99
2		**2k**	>99:1	80	98
3		**2l**	>99:1	68	97
4		**2m**	ND[f]	(<10)	ND[f]
5		**2n**	ND[f]	(94)	14

[a] Reactions were conducted at 65 °C for 24 h, using 1.5 equiv of **4**, 1.5 equiv of Et_3N, 2 mol % of **5** in THF:H_2O 19:1 (10 mL/g of **1a**). [b] As measured by HPLC: peak area percent **2**:**3**. [c] Determined by chiral HPLC analysis of major regioisomer **2** (see the Supporting Information). [d] Isolated yield based upon the average of two separate reactions. Values in parentheses are conversions based upon HPLC peak area percent. [e] Product configuration assigned by analogy to **2e**,**f**. [f] Not determined.

SCHEME 2. Synthesis of Various 4-Alkyl-4-oxobutenamides 1d,e,f



o-halo-substituted boronic acids, an increase in halogen size was accompanied by a decrease in product formation (Cl = 68% yield; Br = <10% conversion; Table 2, entries 3 and 4). The highly electron deficient 2-fluoro-5-(trifluoromethyl)phenylboronic acid **4k** underwent conjugate addition to afford product **2k** in 80% yield, >99:1 regioselectivity (**2k**:**3k**), and 98% ee. The sterically congested 2,6-dimethylphenylboronic acid efficiently underwent conjugate addition to provide **2n** in 94% conversion, however with low enantioselectivity.

Reaction scope with respect to electrophile structure was examined next. Oxobutenamides **1d**−**f** were prepared via the enol-cyclopropanation/ring-expansion method of Zercher[28] (Scheme 2) and subjected to the preferred reaction conditions with complex **5** and boronic acid **4a** (Table 3). Aliphatic oxobutenamides uniformly afforded high regio- and enantioselectivities similar to their aryl counterparts (**1c**,**d** vs **1a**,**b**). The more sterically demanding isopropyl and *tert*-butyl acrylamides (**1e**, **1f**) exhibited lower reactivity compared to other substrates. Increased catalyst loadings and/or switching to a stronger base (potassium hydroxide) was required to achieve synthetically useful yields with these particular substrates.

Variation of the amide structure revealed more profound differences in reaction selectivity. Following the previous trend, *N*,*N*-dialkylamides afforded uniformly high enantio- and regioselectivities (Table 4, entries 1 and 2). While conjugate addition to Weinreb amide **1i** furnished products in high enantioselectivity (97% ee), the regioselectivity was low (2:1) although the desired sense of regiochemistry was still favored. Subjecting monosubstituted amide **1j** to the reaction conditions resulted in a modest reversal of selectivity, now favoring the undesired

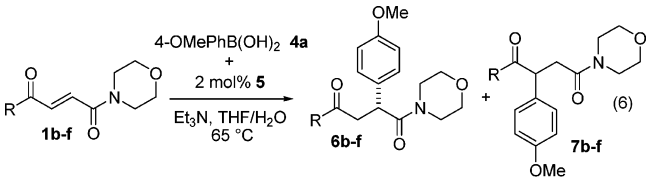
(27) Loss to recrystallization mother liquors was calculated to be 9% of theoretical mass based upon HPLC as calibrated by an external standard (93% assay yield; 100% mass balance).

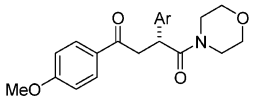
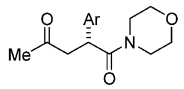
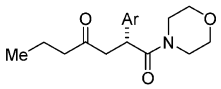
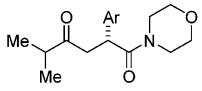
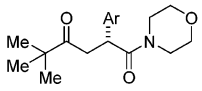
(28) Ronsheim, M. D.; Zercher, C. K. *J. Org. Chem.* **2003**, *68* (11), 4535−4538.

(29) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc*. **2002**, *124* (18), 5052−5058.

(30) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc*. **2007**, *129* (7), 1876−1877.

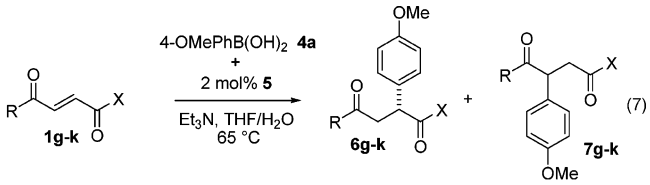
TABLE 3. Effect of Ketone Substituent on Conjugate Addition Reaction of 1 with 4a (eq 6)[a]

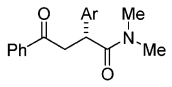
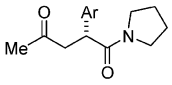
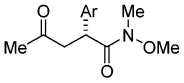
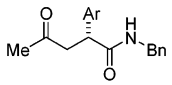
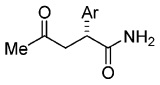


Entry	Structure, Ar = 4-OMePh	Product[d]	6:7[b]	Yield[e]	%ee[c]
1		**6b**	>99:1	97	98
2		**6c**	97:3	90	97
3		**6d**	>95:5[h]	91	99
4		**6e**[f]	>95:5[h]	82	99
5		**6f**[f,g]	>95:5[h]	78	99

[a] Reactions were conducted isothermally at 65 °C for 24 h, using 1.5 equiv of **4a**, 1.5 equiv of Et_3N, 2 mol % of **5**. [b] As measured by HPLC peak area percent **6**:**7**. [c] Determined by chiral HPLC analysis of the major regioismer (see the Supporting Information). [d] Absolute configuration assigned by analogy. [e] Isolated yield based upon the average of two reactions. [f] 10 mol % of catalyst **5** used. [g] KOH (1.5 equiv) was used in place of Et_3N. [h] Ratio as determined by ^1H NMR analysis (authentic standard of regioisomer could not be isolated from the racemic control reaction).

TABLE 4. Effect of Amide Structure on Conjugate Addition Reaction of 1 with 4a (eq 7)[a]



Entry	Structure: Ar = 4-OMePh	Product[d]	6:7[b]	%yield[e]	%ee[c]
1		**6g**	>99:1	89	97
2		**6h**	>99:1	90	99
3		**6i**	2:1	(91)	97
4		**6j**	1:1.3	(60)	97
5		**6k**	ND[g]	ND[g]	ND[g]

[a] Reactions were conducted isothermally at 65 °C for 24 h, using 1.5 equiv of **4a**, 1.5 equiv of Et_3N, 2 mol % of **5**. [b] As measured by HPLC peak area percent **6**:**7**. [c] Determined by chiral HPLC analysis of the major regioismer (see the Supporting Information). [d] Absolute configuration assigned by analogy. [e] Isolated yield based upon the average of two reactions. [f] Regioisomers were not separable by silica gel chromatography. Values in parentheses are combined yields of both regioisomers. [g] Not determined.

conjugate addition product **7j** (Table 4, entry 4), although the enantioselectivity of the desired regioisomer **6j** was still high (97% ee). Primary amide **1k** was unstable under the reaction conditions and no desired product was isolated from the reaction.

Analysis of the product stereochemistry in conjunction with the solid-state structure of precatalyst **5** supports a simple steric model that predicts the stereochemical outcome. On the basis of the generally accepted mechanism of the rhodium-catalyzed conjugate addition,[29] (Figure 3), an aryl rhodium(I) species **9**, generated from transmetallation of the boronic acid,[30] coordinates substrate enone **1** to form complex **10**. Coordination of the substrate is the stereochemical determining step and is followed by irreversible migratory insertion to form a rhodium enolate species **11** that is hydrolyzed to deliver the product and regenerate the active catalytic species **9** (Figure 2). Docking of the substrate to the ligand−arylrhodium complex in proper olefin alignment for migratory insertion shows that coordination of the *si*-face of the substrate places the ketone substiuent away from the sterically bulky *tert*-butyl group on the ligand (Figure 3). Migratory insertion from this intermediate complex would afford the observed *R*-enantiomer. Alternatively, coordination of the olefin from the *re*-face, which results in the opposite enantiomeric product series, forces the ketone substituent into close-contact with the *tert*-butyl group of the phosphine and is expected to be disfavored. While we believe that the high

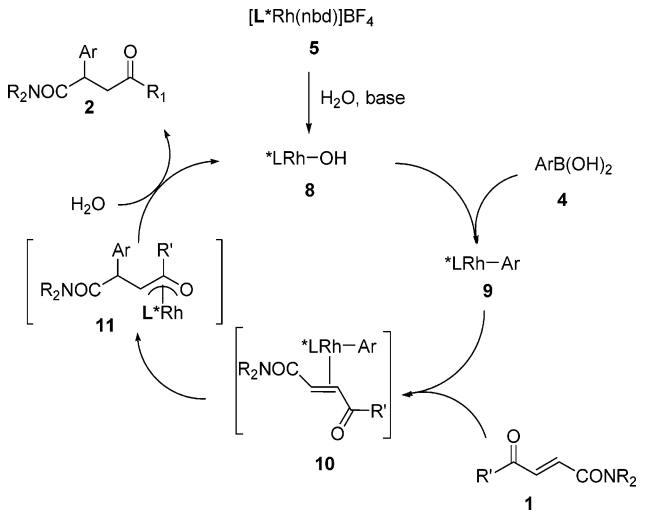


FIGURE 3. Proposed catalytic cycle for rhodium-catalyzed conjugate addition of aryl boronic acids

regioselectivity furnished by this reaction is largely based upon an electronic bias inherent in the starting electrophile, the

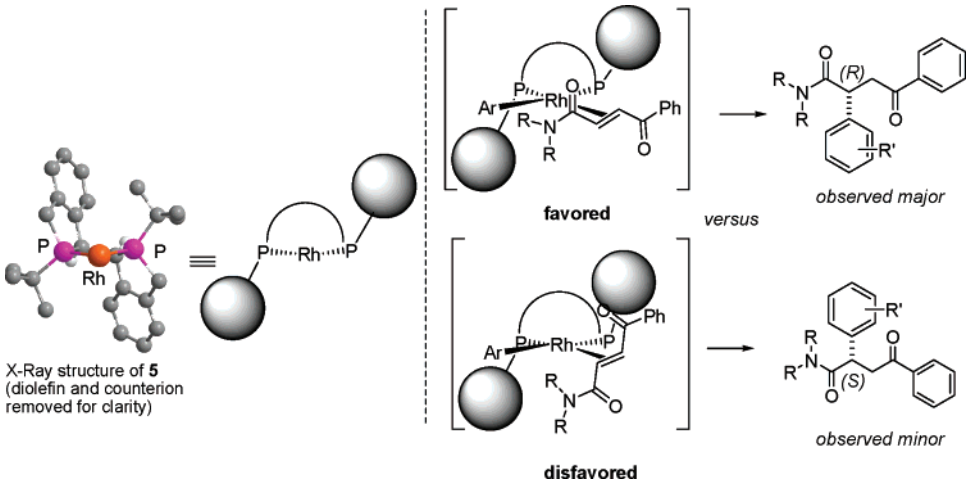
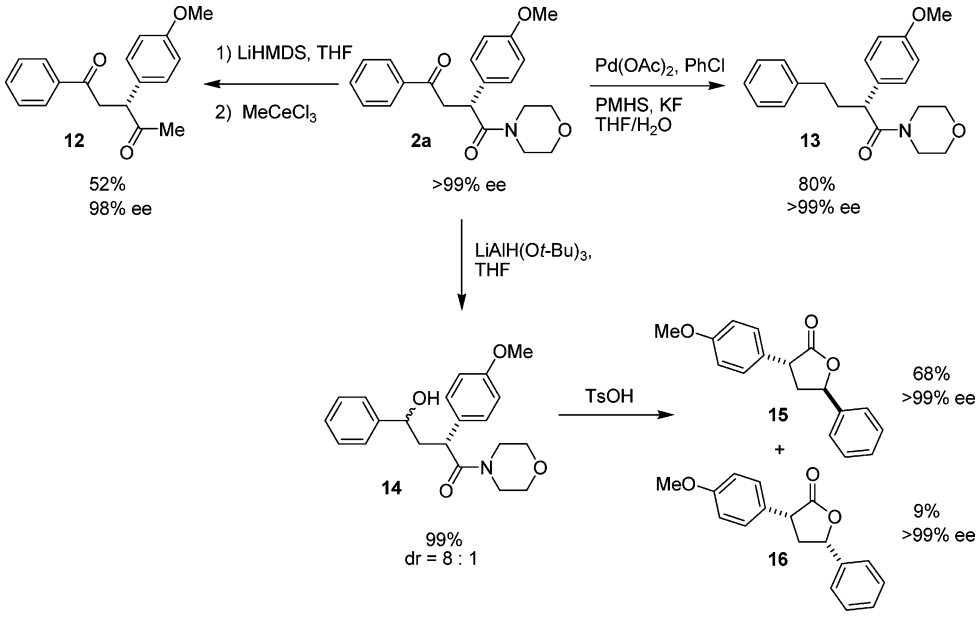


FIGURE 4. Model for prediction of stereochemical outcome in the conjugate addition reaction.

SCHEME 3. Functionalization of Oxobutanamide 2a



observed increase in regioselectivity upon moving to more electron rich phosphine ligands is not well understood and is currently under investigation.

The product oxobutanamides generated from the conjugate addition reaction are synthetically versatile intermediates, and selective manipulation of either the keto or amide functionality may be achieved with minimal erosion of enantiomeric ratio (Scheme 3). For example, diastereoselective reduction of the aryl ketone with lithium *tert*-butoxyaluminum hydride afforded an 8:1 mixture of alcohols that were subjected to acid-mediated cyclization to provide the 2,4-*trans*-disubstituted lactone **15** as the major diastereomer in 68% yield and the minor 2,4-*cis*-disubstituted lactone **16** in 9% yield. The remarkably high optical purities (>99% ee) of both lactone diastereomers confirms that the desired cyclization process is not accompanied by lactone equilibration. Alternatively, in situ protection of the aryl ketone as the corresponding enolate (lithium hexamethyldisilazide), followed by methyl cerium addition to the morpholine amide afforded diketone **12** in 52% yield.[31] Finally, chemoselective palladium-catalyzed deoxygenation of the ketone group[32] under the conditions of Maleckza generated the 4-arylbutanamide **13** in 80% isolated yield with excellent chiral purity. Together, these approaches allow ready access to chiral α-arylamides, ketoamides, diketones, and lactones, many of which are not conveniently prepared by alternative methods.

We have demonstrated that a variety of *N*,*N*-disubstituted 4-oxobutenamides are effective coupling partners with arylboronic acids mediated by a chiral rhodium complex **5**. The reaction is tolerant of various substitution patterns on the boronic acid components and delivers 2-aryl-4-oxobutanamides in high regioselectivity and enantiomeric purity. Structural analysis of product absolute configuration and precatalyst structure affords a simple and predictive stereochemical model for the conjugate addition reaction of these substrates. Investigations into the

(31) Kurosu, M.; Kishi, Y. *Tetrahedron Lett.* **1998**, *39* (27), 4793−4796.

(32) (a) Private correspondence (R. E. Maleczka, Jr.) (b) Rahaim, R. J., Jr.; Maleczka, R. E., Jr. *Palladium Catalyzed Deoxygenations with a Curious Chlorobenzene Effect*; 38th National Organic Chemistry Symposium, June 8−12, Bloomington, IN; The Division of Organic Chemistry of the American Chemical Society: Washington, DC, 2003; Abstract No. C41.

origins of the regioselectivity as well as broadening the substrate scope are underway and will be reported in due course.

Experimental Section

General Procedure for Generation of 4-Oxobutenamides: (*E*)-1-Phenyl-4-morpholinobut-2-ene-1,4-dione (1a). A 500-mL 3-necked round-bottomed flask was charged with (*E*)-4-oxo-4-phenylbut-2-enoic acid (10 g; 56.8 mmol) and 100 mL of anhydrous tetrahydrofuran. The solution was cooled to an internal temperature of −25 to −30 °C whereupon *N*-methylmorpholine (6.9 mL, 62.4 mmol, 1.1 equiv) was added. Isobutyl chloroformate (7.7 mL; 59.6 mmol; 1.05 equiv) was added dropwise maintaining the reaction temperature below −20 °C to form a thick precipitate. The reaction was warmed to 0 °C and stirred 1 h whereupon the reaction was chilled to −20 °C. Morpholine (5.9 mL; 68.1 mmol; 1.2 equiv) was added, and the reaction was warmed to 0 °C and stirred for 1 h. The reaction was quenched with 50 mL of 1 N hydrochloric acid and partitioned into 50 mL of ethyl acetate. The aqueous layer was extracted with 50 mL of methyl *tert*-butyl ether, and the combined organic extracts were washed with 50 mL of 10% aqueous sodium carbonate and then dried over anhydrous magnesium sulfate. The organics were filtered and concentrated to provide a solid. The solid was then suspended in 100 mL of 2:1 methyl *tert*-butyl ether and hexanes. The suspension was stirred for 16 h at ambient temperature, filtered, and then dried to afford 11.1 g of (*E*)-1-phenyl-4-morpholinobut-2-ene-1,4-dione as a yellow solid. Mp 133−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.53 Hz, 2 H), 7.98 (d, J = 15.06 Hz, 1 H), 7.45 (d, J = 14.56 Hz, 1 H), 6.99 (d, J = 9.03 Hz, 2 H), 3.90 (s, 3 H), 3.69−3.83 (m, 6 H), 3.59−3.69 ppm (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.6, 164.2, 134.7, 131.3, 131.0, 129.9, 114.1, 66.8, 55.6, 46.4, 42.6 ppm; HRMS calcd for $C_{15}H_{17}NO_4$ [M + Na] 298.1055, found 298.1067; IR (neat) 2968, 2866, 1667, 1628, 1603, 1448, 1263, 1167, 1032, 831, 761 cm^{-1}.

[(Bicyclo[2.2.1]hepta-2,5-diene)rhodium(I) ((1*S*,1′*S*,2*R*,2′*R*)-2,2′-bis(1,1-dimethylethyl)-2,2′,3,3′-tetrahydro-1,1′-bi-1*H*-isophosphindole)] Tetrafluoroborate (5). In an inert-atmosphere glovebox, a 100-mL Schlenk flask was charged with [bis(bicyclo-[2.2.1]hepta-2,5-dienyl)rhodium(I)] tetrafluoroborate (3.56 g, 9.52 mmol, 1.0 equiv) and 40 mL of dichloromethane. To this solution was added (1*S*,1′*S*,2*R*,2′*R*)-2,2′-bis(1,1-dimethylethyl)-2,2′,3,3′-tetrahydro-1,1′-bi-1*H*-isophosphindole (3.92 g , 10 mmol, 1.05 equiv) in 15 mL of dichloromethane portionwise. The orange solution was stirred at ambient temperature, and the flask was sealed and removed from the glovebox. The dichloromethane was removed in vacuo and redissolved in 20 mL of fresh dichloromethane. This solution was then layered with 40 mL of methyl *tert*-butyl ether and left to crystallize for 12 h. The supernatant was decanted and the crystals were rinsed with 2 × 5 mL of methyl *tert*-butyl ether. A suitable crystal was selected for single-crystal X-ray diffraction analysis (see the Supporting Information, Section VII). The remaining crystals were dried in vacuo and 5.9 g of **5** was isolated as deep red prisms. Analytical data for **5**: mp >230 °C (decomposes); $[\alpha]^{25}_D$ 18.5 (*c* 0.10 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J = 14.56 Hz, 18 H), 1.89 (s, 2 H), 3.41 (dd, J = 17.82, 10.79 Hz, 2 H),3.85 (d, J = 17.57 Hz, 2 H), 4.19 (s, 1 H), 4.24−4.32 (m, 3 H), 5.81 (d, J = 25.60 Hz, 4 H), 7.29−7.42 (m, 6 H), 7.47 ppm (d, J = 7.53 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.9, 55.9, 126.5, 128.1, 128.4, 128.6, 137.9 ppm; ^{31}P NMR (100 MHz, $CDCl_3$) δ 102.9, 103.8 ppm; IR (neat) 2956, 1737, 1579, 1462, 1403, 1368, 1311, 1183, 1033, 829, 789, 769, 754, 677 cm^{-1}.

General Method for the Rhodium-Catalyzed Conjugate Addition Reaction to 4-Oxobutenamides: Preparation of (*R*)-2-(4-Methoxyphenyl)-1-morpholino-4-phenylbutane-1,4-dione (2a). A 20-mL scintillation vial was charged with (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (**1a**) (0.5 g, 2.0 mmol), 4-methoxyphenylboronic acid (456 mg, 3.0 mmol), rhodium catalyst **5** (27 mg, 0.04 mmol), triethylamine (0.42 mL, 3.0 mmol), and tetrahydrofuran/water (19:1, 5 mL). The reaction mixture was warmed to 65 °C and stirred for 16 h. HPLC analysis indicated that the reaction had reached full conversion (99:1 **2a**:**3a**; 98% ee). The crude reaction mixture was poured into 20 mL of ethyl acetate and washed with 10 mL of saturated sodium bicarbonate. The organics were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was analyzed by HLPC[33] (Method A: T_{ret}(**2a**) = 4.3 min, T_{ret}(**3a**) = 4.1 min, >99:1; Method B: T_{ret}(*R*-**2a**) = 1.08 min, T_{ret}(*S*-**2a**) = 1.47 min, 98% ee) and then purified by flash column chromatography (30% to 100% ethyl acetate in hexanes) to afford the product as a colorless solid (701 mg, 96%). Mp (133−135 °C). $[\alpha]^{25}_D$ −157.4 (*c* 1.2 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.53 Hz, 2 H), 7.44 (t, J = 7.53 Hz, 2 H), 7.55 (t, J = 7.28 Hz, 2 H), 7.16−7.31 (m, 2 H), 6.89 (d, J = 8.53 Hz, 2 H), 4.49 (dd, J = 9.79, 3.76 Hz, 1 H), 4.10 (dd, J = 17.82, 9.79 Hz, 1 H), 3.81 (s, 3 H), 3.76−3.33 (m, 7 H), 3.30−3.12 (m, 1 H), 3.06 ppm (dd, J = 17.57, 3.51 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7, 171.1, 158.8, 136.6, 133.1, 131.2, 128.7, 128.5, 128.2, 114.5, 66.8, 66.4, 55.3, 46.2, 44.3, 43.2, 42.6; HRMS calcd for $C_{21}H_{24}NO_4$ $[M]^+$ 354.1699, found 354.1748; IR (neat) 2972, 2856, 1698, 1628, 1606, 1502, 1441, 1231, 1024, 829 cm^{-1}.

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Supporting Information Available: Catalyst screening table, general methods, chromatographic methods, characterization data, NMR spectra, and single-crystal diffraction data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(33) See the Supporting Information for details.