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A rapid catalytic asymmetric synthesis of 1,3,4-trisubstituted pyrrolidines ☆

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Abstract—The asymmetric synthesis of 1,3,4-trisubstituted pyrrolidines was accomplished in two steps from readily available starting materials. A 1,3-dipolar cycloaddition of an azomethine ylide to a propiolate ester followed by a Rh-catalyzed asymmetric 1,4-arylation of the resulting pyrroline with an arylboronic acid provided the desired 1,3,4-trisubstituted pyrrolidine products in good to excellent enantioselectivities.
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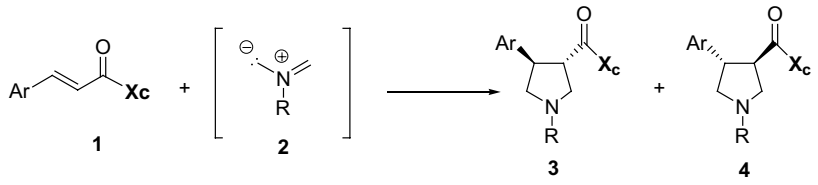
Substituted pyrrolidines are structural motifs found in numerous natural products and biologically active compounds.[1] One such class of compounds recently identified by Merck as CCR5 antagonists with potent anti-HIV activity is a series of chiral 1,3,4-trisubstituted pyrrolidines.[2] This substitution pattern is also prevalent in a series of recently reported pyrrolidine-based monoamine transporter inhibitors,[3] coagulation factor X_a inhibitors,[4] and endothelin receptor antagonists.[5] Given their importance, we desired to develop a rapid asymmetric synthesis of these chiral pyrrolidines from readily available starting materials.

One of the most direct and widely used methods for the preparation of substituted pyrrolidines, as outlined in Scheme 1, involves a 1,3-dipolar cycloaddition of non-stabilized azomethine ylide **2** to an α,β-unsaturated dipolarophile **1**.[6] An asymmetric variant of this reaction utilizes oxazolidinone or camphorsultam-based chiral auxiliaries $\mathbf{X_c}$ appended to the dipolarophile. This auxiliary-based approach was shown to give 1,3,4-trisubstituted pyrrolidine cycloadducts **3** and **4** with modest diastereoselectivity (up to 48% de).[7] A recent report utilizing both a chiral auxiliary and chiral azomethine ylide (where R contains a stereogenic center) provided a slight increase in selectivity.[8] Indeed, our initial investigations using these approaches verified that the camphorsultam-based chiral auxiliary provided the best results. However, several limitations of the chiral auxiliary-based approach (e.g. added steps to append and remove the chiral auxiliary, modest selectivities, and chromatography required to separate the undesired



Scheme 1.

Keywords: Pyrrolidine; 1,3-Dipolar cycloaddition; Asymmetric 1,4-addition; Rhodium-catalyzed; Arylboronic acid.
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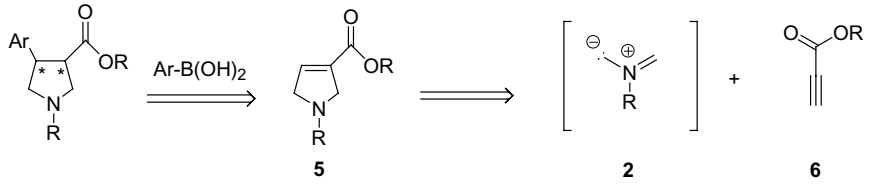
diastereomer) prompted us to develop a catalytic method for the preparation of these chiral pyrrolidines.

Our retrosynthetic analysis of 1,3,4-trisubstituted pyrrolidines is shown in Scheme 2. Pyrroline **5** can be obtained via 1,3-dipolar cycloaddition of azomethine ylide **2** with propiolate ester **6**.[9] Asymmetric 1,4-arylation of **5** could subsequently be accomplished with an arylboronic acid[10] to afford the nonracemic 1,3,4-trisubstituted pyrrolidines. This novel two step catalytic route is attractive due not only to the readily available starting materials, but to the ability to prepare either chiral antipode simply by selecting the appropriate enantiomer of the chiral ligand.

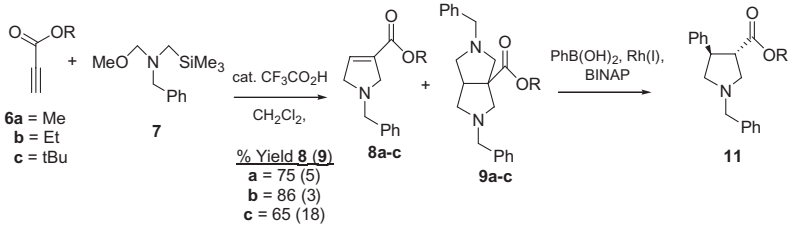
A variety of substituted pyrroline esters were prepared, as shown in Scheme 3, under acid-catalyzed 1,3-dipolar cycloaddition conditions utilizing commercially available *N*-benzyl-*N*-(methoxymethyl)-trimethylsilylmethylamine (**7**) as the azomethine ylide source and commercially available propiolate esters as dipolarophiles.[9] Protected azomethine precursor **7** was chosen because of its availability and the mild conditions under which the ylide can be generated. The unsaturated esters were found to be both air and thermally sensitive.[11] While both **8a** and **8b** were found to be unstable oils,[12] *t*-butyl ester **8c** could be obtained as a stable solid with excellent purity after a single crystallization. Formation of a significant amount of double cycloaddition adduct **9** was observed in the case of **8c**.

The Rh-catalyzed 1,4-conjugate addition of phenylboronic acid to **8c** was subsequently investigated in the presence of a variety of Rh(I) catalysts and different solvents. The results of these studies are shown in Table 1.

The 1,4-addition reaction provided the desired 1,3,4-trisubstituted pyrrolidine **11c** in only 13% yield when using conditions similar to those reported by Miyuara and co-workers (entry 1).[13] The reaction was sluggish and **8c** was found to be unstable at high reaction temperatures. The use of $[Rh(Cl)(C_2H_2)]_2$/BINAP and KOH in place of $Rh(acac)(C_2H_2)_2$/BINAP, gave slightly



Scheme 2.

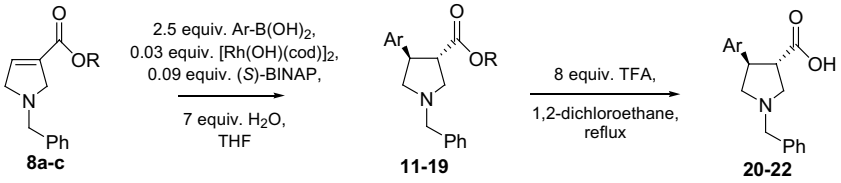


Scheme 3.

Table 1. Catalyst screening experiments for the Rh(I)/BINAP-catalyzed 1,4-addition of $PhB(OH)_2$ to **8c**.

Entry	Rh catalyst[a]	Temperature (°C)[b]	Solvent[c]	Time (h)	Assay yield **11c**[d] (%)[e]
1	$Rh(acac)(C_2H_2)_2$	100	Dioxane/H_2O	16	13
2	$[Rh(Cl)(C_2H_2)]_2$[f]	50	Dioxane/H_2O	16	36
3	$[Rh(Cl)(C_2H_2)]_2$	75	Dioxane/H_2O	16	34
4	$[Rh(Cl)(C_2H_2)]_2$	50	THF/H_2O	16	21
5	$[Rh(OH)(cod)]_2$	50	Dioxane/H_2O	16	92
6	$[Rh(OH)(cod)]_2$	50	THF/H_2O	16	95 (70)[g]
7	$[Rh(OH)(cod)]_2$	50	$(EtOCH_2)_2$/H_2O	16	51

[a] All experiments were run in the presence of 0.06 equiv Rh, 0.09 equiv BINAP, and 2.5 equiv $PhB(OH)_2$.
[b] Oil bath temperature in which reaction flask was immersed in.
[c] All experiments were run in the presence of 7 equiv H_2O and at a concentration of 0.2 M.
[d] Assay yield was determined by HPLC versus an external standard solution of the purified substrate.
[e] Isolated yield in parenthesis.
[f] KOH (0.06 equiv) was used as an additive.
[g] Isolated yield reported is the average of three runs.



Scheme 4.

Table 2. Results for the Rh-catalyzed 1,4-addition of $ArB(OH)_2$ to **8a–c** and saponification

Entry	Ar–B(OH)$_2$ Ar =	Temperature (°C)[a]	Time (h)	Isolated yield (% ee)[b] **11–19**	Isolated yield[c] (% ee)[d] **20–22**
1[e]	3-F–C_6H_4	100	16	51 (65) **12a**	
2[e]	3-F–C_6H_4	100	16	55 (81) **12b**	
3[e]	3-F–C_6H_4	100	16	28 (91) **12c**	
4	3-F–C_6H_4	50	4	74 (96) **12c**	
5	Ph	50	4	70 (95) **11c**	85 (96) **20**
6	4-CH_3–C_6H_4	50	4	76 (89) **13c**	78 (89) **21**
7	3-CF_3–C_6H_4	50	24	23 (95) **14c**	
8	4-OMe–C_6H_4	50	19[f]	52 (78) **15c**	92 (78) **22**
9	4-Cl–C_6H_4	50	19	87 (84) **16c**	
10	2-Napthelene	50	19	79 (85) **17c**	
11	1-Napthelene	50	19	No rxn **18c**	
12	2-CH_3–C_6H_4	50	19	10 (-) **19c**	

[a] Oil bath temperature in which reaction flask was immersed in.
[b] ee Determined by HPLC analysis of the isolated substrate on a chiral column.
[c] Overall isolated yield from **8c**.
[d] ee Determined by SFC analysis of the isolated substrate on a chiral column.
[e] $Rh(acac)(C_2H_2)_2$ (0.06 equiv) was used as catalyst and dioxane/H_2O as solvent.
[f] Another 0.03 equiv of $[Rh(OH)(cod)]_2$ was added to the reaction after 4 h.

improved results (entry 2).[14] Increasing the reaction temperature did not improve the yield (entry 3). Replacing dioxane with THF as solvent also did not improve the yield (entry 4). It was ultimately found that use of $[Rh(OH)(cod)]_2$/BINAP gave the best results for the 1,4-addition (entries 5–7).[15] Use of THF/H_2O as solvent with this catalyst provided the highest assay yields (typically 89–98%). Isolation of **11c**, however, proved difficult. Pyrrolidine **11c** was found to be unstable to silica gel and alumina chromatography. For example, a 20–30% loss of **11c** was observed over silica gel chromatography. However, direct saponification of the crude ester to the carboxylic acid provided a stable pyrrolidine intermediate that could be purified by crystallization. The addition of a saponification step also provides a substrate that can be readily esterified, coupled or reduced.

We next investigated the scope of the asymmetric 1,4-addition reaction, as outlined in Scheme 4. A variety of arylboronic acids were examined in the 1,4-addition and some of the resulting crude pyrrolidine esters were converted directly to their corresponding free carboxylic acids. The results of these studies are summarized in Table 2.

The enantioselectivity for the 1,4-addition was observed to increase with the steric bulkiness of the propiolate ester (entries 1–3). It was found that the Rh-catalyzed 1,4-addition worked well with either electron neutral arylboronic acids, electron-rich arylboronic acids, and with electron-deficient arylboronic acids under the optimized conditions.[16] The 1,4-addition reaction, however, did not work with sterically hindered boronic acids (entries 11 and 12). Direct saponification of the crude 1,4-addition adduct to the corresponding carboxylic acid provided a higher overall yield of the 1,4-addition adduct from **8c** in certain cases (entries 20–22). The *trans* geometry of **20** was confirmed by NOE. The absolute configuration was not determined.

In summary, we have demonstrated the rapid asymmetric synthesis of 1,3,4-trisubstituted pyrrolidines in two steps utilizing readily available starting materials. A series of pyrroline derivatives were prepared via 1,3-dipolar cycloaddition and subsequently found to undergo Rh-catalyzed asymmetric 1,4-addition with a variety of arylboronic acids in moderate to good isolated yields and in excellent enantioselectivities. The results reported herein represent a completely new application of the Rh-catalyzed asymmetric 1,4-addition reaction as well as an improved method for the asymmetric synthesis of 1,3,4-disubstituted pyrrolidines.

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16. Pyrrolidine **11c** was prepared as follows: Phenylboronic acid (1.18 g, 9.6 mmol), (*S*)-Binap (220 mg, 0.35 mmol), $[Rh(OH)(cod)]_2$ (52 mg, 0.1 mmol), and **8c** (1.0 g, 3.8 mmol) were charged to a Schlenk tube, purged with Argon, and then diluted with THF (23 mL) and water (490 μL, 27 mmol). The resulting deep-red solution was warmed to 50 °C for 16 h and then quenched with sat. $NaHCO_3$ (70 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (100 mL). The organic layer was concentrated and the oil purified by flash chromatography (SiO_2, 10% EtOAc:hexanes) to provide **11c** in 71% yield as a colorless oil (1.06 g). ^1H NMR: (400 MHz, $CDCl_3$): δ 7.2–7.5 (10H, m), 3.6–3.9 (4H, m); 3.00–3.15 (2H, m), 2.9 (1H, m), 3.7 (1H, m). ^{13}C NMR ($CDCl_3$): δ 28.16, 47.20, 52.86, 57.46, 60.07, 61.92, 80.61, 126.46, 127.06, 127.59, 128.35, 128.52, 128.72, 139.06, 144.61, 173.45. Alternatively, the crude reaction mixture could be directly saponified as follows: TFA (2.3 mL, 30 mmol) was added to a solution of crude **11c** (1.2 g, 3.6 mmol) in 1,2-dichloroethane (15 mL) and heated at reflux for 6 h. Aqueous NaOH (1 N) was added at 20 °C until the pH of the aqueous phase measured 6.8. The layers were separated and the organic layer concentrated to ~2 mL, at which point acetone (10 mL) was added to complete precipitation of **20**. The suspension was filtered and the solids washed with 2×5 mL of water. The white solid was dried under vacuum to provide 910 mg of *trans*-1-benzyl-4-phenylpyrrolidine-3-carboxylic acid (**20**) in 85% overall yield from **8c**. ^1H NMR (500 MHz, CD_3OD): δ 7.52 (m, 2H), 7.44–7.41 (om, 3H), 7.36 (m, 2H), 7.31 (m, 2H), 7.24 (m, 1H), 4.34 (AB doublet, $\Delta\nu = 6.2$, 2H), 3.85 (dt, $J = 10.7$, 8.3 Hz, 1H), 3.70 (dd, $J = 10.7$, 8.3 Hz, 1H), 3.57 (d, $J = 8.3$ Hz, 2H), 3.27 (t, $J = 10.7$ Hz, 1H), 3.20 (q, $J = 8.3$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ 177.91, 140.96, 133.30, 131.50, 130.74, 130.37, 130.00, 128.75, 128.54, 61.10, 59.89, 58.55, 53.49, 48.55 ppm. Results for all NOE experiments can be found in the Supplementary data section.