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Successive Nucleophilic and Electrophilic Allylation for The Catalytic Enantioselective Synthesis of 2,4-Disubstituted Pyrrolidines

Guoshun Luo, Ming Xiang, and Michael J. Krische

University of Texas at Austin, Department of Chemistry, Austin, TX 78712

Abstract

Successive nucleophilic and electrophilic allylation mediated by the bis-Boc-carbonate derived from 2-methylene-1,3-propane diol enables formation of enantiomerically enriched 2,4-disubstituted pyrrolidines. An initial enantioselective iridium-catalyzed transfer hydrogenative carbonyl *C*-allylation is followed by Tsuji-Trost *N*-allylation using 2-nitrobenzenesulfonamide. Subsequent Mitsunobu cyclization provides the *N*-protected 2,4-disubstituted pyrrolidines.

Graphical Abstract

The development of catalytic asymmetric methods for the synthesis of saturated *N*-heterocycles^{1,2} is driven by the frequency with which such structural motifs occur as substructures in FDA approved drugs,³ and the growing appreciation that stereochemical complexity improves prospects for clinical success.^{4,5} Our exploration of hydrogen-mediated reductive coupling⁶ has enabled diverse methods for catalytic enantioselective C-C bond formation, including carbonyl allylation.^{6d,7} In these processes, primary alcohol oxidation is balanced by C-O reductive cleavage of an allylic acetate pronucleophile resulting in the formation of a transient aldehyde-allylmetal pair, which combine to form secondary homoallylic alcohols. Based on this reactivity pattern, we envisioned an approach to *N*-protected 2,4-disubstituted pyrrolidines wherein the *bis*-Boc-carbonate derived from 2-methylene-1,3-propane diol is subjected to successive nucleophilic and electrophilic

Corresponding Author. mkrische@mail.utexas.edu.

Notes.

The authors declare no competing financial interest.

Supporting Information Available. Spectral data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS). Single crystal X-ray diffraction data for compounds **3i** and **7d**. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

allylation (Figure 1).^{8,9} While numerous bifunctional allylmetal reagents based on tin, boron or silicon have been described,¹⁰ the use of such reagents for pyrrolidine synthesis is uncommon and is solely manifested by the pioneering efforts of Trost *vis-à-vis* trimethylenemethane (TMM) cycloadditions of imines.^{10a,11,12} Catalytic enantioselective cycloadditions of this type have been reported,^{11c-f} but require tailored chiral phosphoramidite ligands and are largely restricted to aryl-substituted imines.^{11c,e} To our knowledge, highly enantioselective syntheses of 2-alkyl-4-methylenepyrrolidines remain a largely unmet challenge. Here, we report a catalytic protocol for the synthesis of 2-alkyl-4-methylenepyrrolidines that utilizes inexpensive SEGPHOS ligands and avoids moisture sensitive imine reactants.

In an initial experiment, 4-bromobenzyl alcohol **1a** (100 mol %) was exposed to *bis*-Boc-carbonate **2a**¹³ (200 mol %) in the presence of the π -allyliridium *C,O*-benzoate complex derived from 4-cyano-3-nitrobenzoic acid and (*S*)-DM-SEGPHOS and K₃PO₄ (100 mol %) in DME (0.4 M) at 80 °C. The homoallylic alcohol **3a** was generated in 58% yield and 89% ee (Table 1, entry 1). Decreased loadings of K₃PO₄ (10 mol %) led to a higher isolated yield of **3a** (Table 1, entry 3). Different chiral phosphine ligands were evaluated (Table 1, entries 6–9). Optimal enantioselectivities were obtained using (*S*)-DM-SEGPHOS or (*S*)-SEGPHOS (Table 1, entries 3 and 9). It was found that a slight decrease in reaction temperature (70 °C) improved enantioselectivity without diminishing the isolated yield of **3a** (Table 1, entry 11). Similar efficiencies were observed with the catalyst incorporating the 3,4-dinitro-*C,O*-benzoate moiety (Table 1, entry 12).

As 3,4-dinitrobenzoic acid is commercially available (and 4-cyano-3-nitrobenzoic acid is not), the optimized conditions employing (*S*)-**Ir-III** (Table 1, entry 12) were applied to the coupling of alcohols **1a–1j** with *bis*-Boc-carbonate **2a** (Table 2). Benzylic alcohols **1a–1e**, the allylic alcohol geraniol **1f**, and aliphatic alcohols **1g–1j** delivered the respective adducts **3a–3j** in good yield with excellent levels of enantioselectivity. The absolute stereochemistry of adducts **3a–3j** was assigned in analogy to adduct **3i**, which was determined by single crystal X-ray diffraction analysis. The conversion of alcohols **1a–1j** to adducts **3a–3j** represent redox-neutral processes. As illustrated by the conversion of aldehydes *dehydro-1e*, *dehydro-1f* and *dehydro-1h* to adducts **3e**, **3f** and **3h**, 2-propanol-mediated reductive couplings of aldehyde reactants also proceed efficiently with high levels of enantioselectivity under identical conditions (Scheme 1).

The conversion of adducts **3a–3j** to the 2-substituted 4-methylenepyrrolidines **5a–5j** was achieved via Tsuji-Trost allylation followed by Mitsunobu cyclization (Table 3). Whereas Tsuji-Trost allylation of *para*-nitrobenzenesulfonamide resulted in significant quantities of over-alkylation, corresponding reactions of *ortho*-nitrobenzenesulfonamide were more selective, providing the highly tractable *ortho*-nosyl containing adducts **4a–4j** in good yield.¹⁴ Cyclization of adducts **4a–4j** under Mitsunobu conditions proceeded smoothly to deliver the 2-substituted 4-methylenepyrrolidines **5a–5j**.¹⁵ The enantiomeric purity of 2 pyrrolidines **5d** and **5j** was evaluated, which revealed no erosion in enantiomeric purity occurred upon Mitsunobu cyclization.

To illustrate the utility of 4-methylenepyrrolidines **5a–5j**, compounds **5d** and **5h** were subjected to a series of functional group manipulations (Scheme 2). The synthesis of carboxamide **7d** from compound **5d** demonstrates facile removal of the *ortho*-nosyl protecting group and corroborates the anticipated inversion of stereochemistry in the Mitsunobu cyclization.¹⁵ 4-Methylenepyrrolidine **5h** is readily converted to the spirocyclopropane **6h**,¹⁶ which embodies a structural motif evident in the FDA approved drug for the treatment of hepatitis C.¹⁷ Finally, oxidative cleavage¹⁸ of 4-methylenepyrrolidine **5h** followed by exposure of the resulting ketone **7h** to Deoxy-Fluor®¹⁹ delivers the *gem*-difluoride **8h**.

In conclusion, we report the enantioselective synthesis of 2-substituted-4-methylenepyrrolidines through successive nucleophilic and electrophilic allylation of *bis*-Boc-carbonate **2a**. Whereas prior methods for the enantioselective synthesis of 2-substituted-4-methylenepyrrolidines involve TMM cycloadditions of moisture sensitive imine reactants and are restricted to 2-aryl-substituted adducts, the present protocol enables facile access to 2-alkyl-4-methylenepyrrolidines from highly tractable alcohol reactants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Enantioselective pyrrolidine synthesis via successive nucleophilic and electrophilic allylation.

Scheme 1.

Reductive coupling of aldehydes *dehydro-1e*, *dehydro-1f* and *dehydro-1h* with bis-Boc-carbonate **2a** to form adducts **3e**, **3f** and **3h**.^a

Scheme 2.

Derivatization of 4-methylenepyrrolidines **5d** and **5h**.^a

Table 1.

Selected optimization experiments in the enantioselective coupling of alcohol **1a** and *bis*-Boc-carbonate **2a** via alcohol-mediated hydrogen transfer.^a

1a, R = *p*-BrPh
(100 mol %)

2a
(200 mol %)

catalyst (5 mol %)

K_3PO_4 , DME (0.4 M)

T °C

3a

entry	catalyst	T °C	K ₂ PO ₄ (mol %)	yield (%)	ee (%)
1	(<i>S</i>)-Ir-II	80	100	58	89
2	(<i>S</i>)-Ir-II	80	50	69	90
3	(<i>S</i>)-Ir-II	80	10	76	90
4	(<i>S</i>)-Ir-II	80	5	59	90
5	(<i>S</i>)-Ir-II	80	0	Trace	---
6	(<i>S</i>)-Ir-IV	80	10	48	65
7	(<i>S</i>)-Ir-V	80	10	43	55
8	(<i>S</i>)-Ir-VI	80	10	53	69
9	(<i>S</i>)-Ir-I	80	10	66	90
10	(<i>S</i>)-Ir-II	60	10	70	98
11	(<i>S</i>)-Ir-II	70	10	77	96
12	(<i>S</i>)-Ir-III	70	10	76	96

(*S*)-Ir-I, Ar = Ph, R = CN

(*S*)-Ir-IV, Ar = Ph

(*S*)-Ir-VI

(*S*)-Ir-II, Ar = 3,5-Me₂Ph, R = CN

(*S*)-Ir-V, Ar = 4-MePh

(*S*)-Ir-III, Ar = 3,5-Me₂Ph, R = NO₂

^aYields are of material isolated by silica gel chromatography. Enantioselectivity was determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

Table 2.

Redox-neutral coupling of alcohols **1a–1j** with *bis*-Boc-carbonate **2a** to form adducts **3a–3j**.^a

^aYields are of material isolated by silica gel chromatography. Enantioselectivity was determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

^b(*S*)-**Ir-II** (5 mol %).

^cDME (0.2 M), 60 °C.

Table 3.

Conversion of adducts **3a–3j** to 4-methylenepyrrolidines **5a–5j** via Tsuji-Trost allylation-Mitsunobu cyclization.^a

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

^bAfter the first reaction was done, PPh₃ (500 mol %), DIAD (500 mol %) and THF (0.05 M) were added at 25 °C, 12 h.