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

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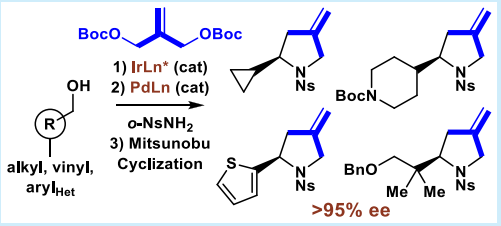
Supporting Information

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.



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 coupling[6] 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 allylation (Figure 1).[8,9] While

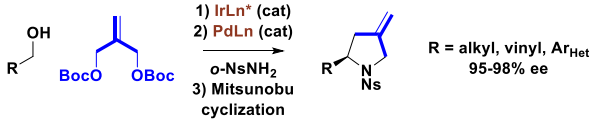


Figure 1. Enantioselective pyrrolidine synthesis via successive nucleophilic and electrophilic allylation.

numerous related 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 only known in the context of Trost's pioneering work on imine-mediated trimethylenemethane (TMM) cycloadditions.[10a,11,12] Catalytic enantioselective cycloadditions of this type have been reported using phosphoramidite-modified palladium catalysts.[11c–f] However, while high enantioselectivities are observed in TMM cycloadditions of aryl-substituted imines,[11c,e] the construction of 2-alkyl-4-methylenepyrrolidines in highly enantiomerically enriched form remains a largely unmet challenge. Here, utilizing an iridium catalyst modified by an inexpensive, commercially available ligand, SEGPHOS, we report a catalytic protocol for the synthesis of diverse 2-substituted-4-methylenepyrrolidines, including 2-alkyl derivatives, that avoids the use of 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 K_3PO_4 (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 K_3PO_4 (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–j** with *bis*-Boc-carbonate **2a** (Scheme 1). Benzylic alcohols **1a–e**, the allylic alcohol geraniol **1f**, and aliphatic alcohols **1g–j** delivered the respective adducts **3a–j** in good yield with excellent levels of enantioselectivity. The absolute stereochemistry of adducts **3a–j** was assigned in analogy to adduct **3i**, which was determined by single-crystal X-ray diffraction analysis. The conversion of alcohols **1a–j** to adducts **3a–j** represents 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

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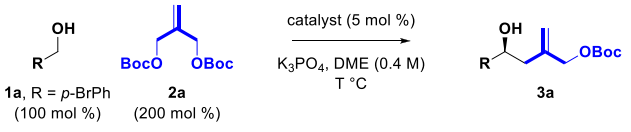
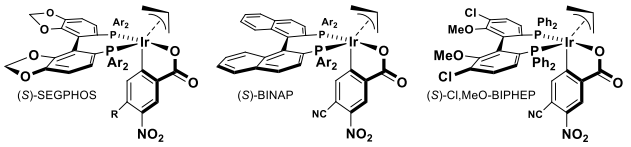
Table 1. Selected Optimization Experiments in the Enantioselective Coupling of Alcohol 1a and *bis*-Boc-carbonate 2a via Alcohol-Mediated Hydrogen Transfer[a]



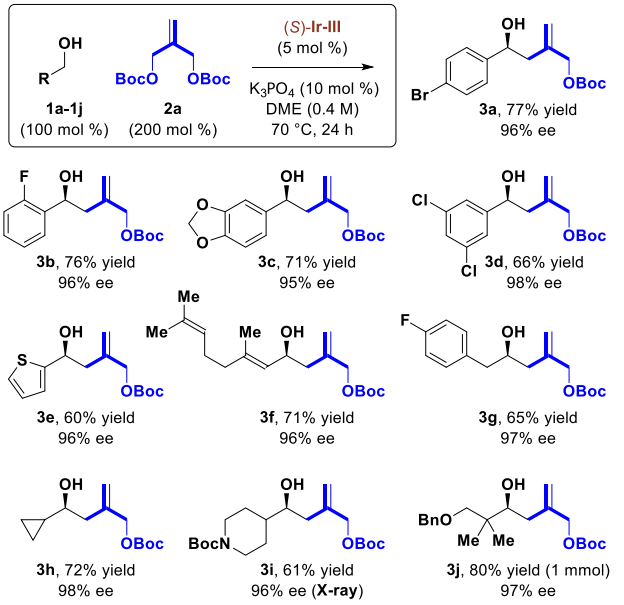
entry	catalyst	T °C	K_3PO_4 (mol %)	yield (%)	ee (%)
1	(*S*)-**Ir-II**	80	100	58	89
2	(*S*)-**Ir-II**	80	50	69	90
3	(*S*)-**Ir-II**	80	10	76	90
4	(*S*)-**Ir-II**	80	5	59	90
5	(*S*)-**Ir-II**	80	0	Trace	---
6	(*S*)-**Ir-IV**	80	10	48	65
7	(*S*)-**Ir-V**	80	10	43	55
8	(*S*)-**Ir-VI**	80	10	53	69
9	(*S*)-**Ir-I**	80	10	66	90
10	(*S*)-**Ir-II**	60	10	70	98
11	(*S*)-**Ir-II**	70	10	77	96
12	(*S*)-**Ir-III**	70	10	76	96



(*S*)-**Ir-I**, Ar = Ph, R = CN
(*S*)-**Ir-II**, Ar = 3,5-Me_2Ph, R = CN
(*S*)-**Ir-III**, Ar = 3,5-Me_2Ph, R = NO_2
(*S*)-**Ir-IV**, Ar = Ph
(*S*)-**Ir-V**, Ar = 4-MePh
(*S*)-**Ir-VI**

[a]Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary-phase HPLC analysis. See the Supporting Information for further experimental details.

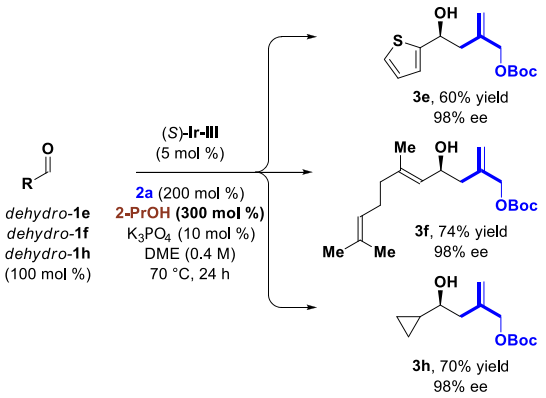
Scheme 1. Redox-Neutral Coupling of Alcohols 1a–j with *bis*-Boc-carbonate 2a To Form Adducts 3a–j[a]



[a]Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary-phase HPLC analysis. For compounds **3a**, **3b**, and **3d**, (*S*)-**Ir-II** was used as catalyst. See the Supporting Information for further experimental details.

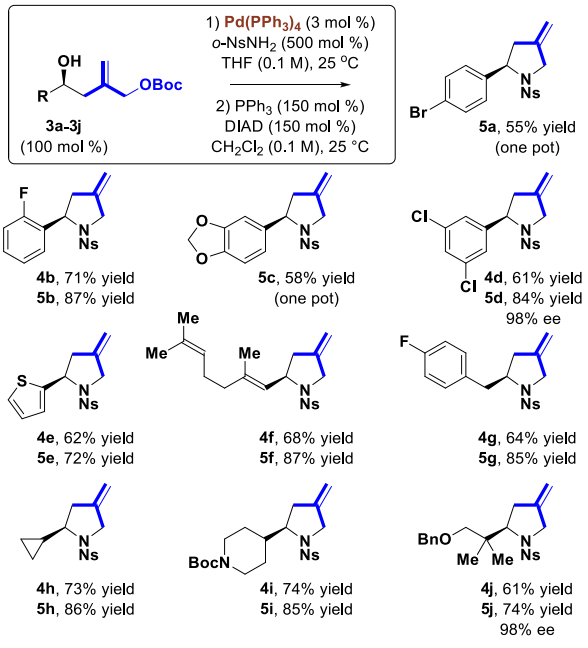
efficiently with high levels of enantioselectivity under identical conditions (Scheme 2).

Scheme 2. Reductive Coupling of Aldehydes *dehydro*-1e, *dehydro*-1f, and *dehydro*-1h with *bis*-Boc-carbonate 2a To Form Adducts 3e, 3f and 3h[a]



[a]Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See the Supporting Information for further experimental details.

Scheme 3. Conversion of Adducts 3a–j to 4-Methylenepyrrolidines 5a–j via Tsuji–Trost Allylation–Mitsunobu Cyclization[a]



[a]Yields are of material isolated by silica gel chromatography. See the Supporting Information for further experimental details.

The conversion of adducts **3a–j** to the 2-substituted 4-methylenepyrrolidines **5a–j** was achieved via Tsuji–Trost allylation followed by Mitsunobu cyclization (Scheme 3). Whereas Tsuji–Trost allylation of *p*-nitrobenzenesulfonamide resulted in significant quantities of overalkylation, corresponding reactions of *o*-nitrobenzenesulfonamide were more selective, providing the highly tractable *o*-nosyl-containing adducts **4a–j** in good yield.[14] Cyclization of adducts **4a–j** under Mitsunobu conditions proceeded smoothly to deliver the 2-substituted 4-methylenepyrrolidines **5a–j**.[15] The enantiomeric purity of 2 pyrrolidines **5d** and **5j** was evaluated,

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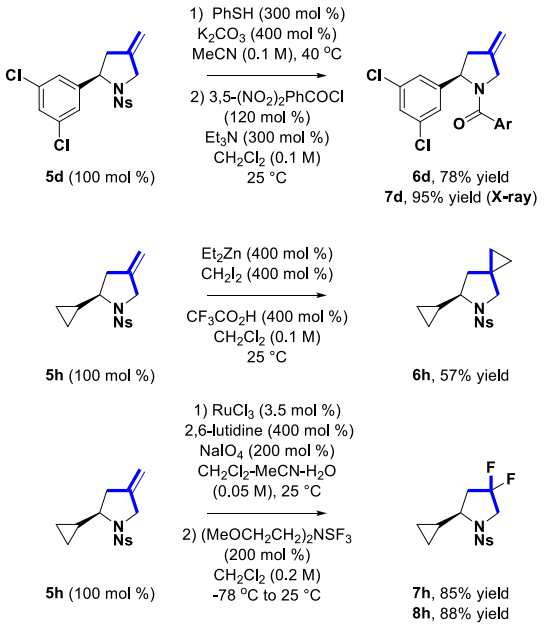
which revealed no erosion in enantiomeric purity occurred upon Mitsunobu cyclization.

Scheme 4. Derivatization of 4-Methylenepyrrolidines 5d and 5h[a]



[a]Yields are of material isolated by silica gel chromatography. See the Supporting Information for further experimental details.

To illustrate the utility of 4-methylenepyrrolidines **5a–j**, compounds **5d** and **5h** were subjected to a series of functional group manipulations (Scheme 4). The synthesis of carboxamide **7d** from compound **5d** demonstrates facile removal of the *o*-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 an FDA-approved drug for the treatment of hepatitis C.[17] Finally, oxidative cleavage[18] 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 enantioselective syntheses of 2-substituted-4-methylenepyrrolidines through successive nucleophilic and electrophilic allylations 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 largely restricted to 2-aryl-substituted adducts, the present protocol enables facile access to both 2-aryl- and 2-alkyl-4-methylenepyrrolidines from highly tractable primary alcohol reactants.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00508.

Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). Single-crystal X-ray diffraction data for compounds **3i** and **7d** (PDF)

Accession Codes

CCDC 1895865–1895866 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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