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Nickel-Catalyzed Asymmetric Reductive Cross-Coupling Between Vinyl and Benzyl Electrophiles

Alan H. Cherney and Sarah E. Reisman*

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Supporting Information

ABSTRACT: A Ni-catalyzed asymmetric reductive cross-coupling between vinyl bromides and benzyl chlorides has been developed. This method provides direct access to enantioenriched products bearing aryl-substituted tertiary allylic stereogenic centers from simple, stable starting materials. A broad substrate scope is achieved under mild reaction conditions that preclude the pregeneration of organometallic reagents and the regioselectivity issues commonly associated with asymmetric allylic arylation.

Ni-catalyzed reductive cross-coupling reactions have recently emerged as direct methods for carbon−carbon bond formation between two organic electrophiles.[1] In these reactions, Mn^0 or Zn^0 are typically employed as stoichiometric reductants to turn over a Ni catalyst. Improvements in ligand structure and mechanistic understanding have enabled the cross-coupling between a range of $C(sp^3)$ and $C(sp^2)$ electrophiles bearing a variety of functional groups.[2−4] The ability to employ bench stable and readily available organic halides, without the need to pregenerate a reactive organometallic reagent, endows these reductive cross-coupling reactions with a practical advantage over many conventional cross-coupling procedures. In addition, several studies have demonstrated that *sec*-alkyl electrophiles are competent reaction partners, providing racemic products bearing stereogenic centers.[2a,b,d,e,h,3a,5] The utility of such transformations would be greatly improved if rendered enantioselective, providing direct access to enantioenriched chiral products from racemic starting materials.[6]

Alkenes bearing stereogenic, aryl-substituted tertiary allylic centers are synthetically useful compounds that can be challenging to prepare using conventional asymmetric allylic substitution reactions (Figure 1a).[7,8] Significant progress toward the catalytic enantioselective arylation of allylic electrophiles has been made to selectively form branched over linear *mono*-substituted products.[9] Stereospecific and regioselective arylation of allylic electrophiles to form *di*substituted products has also been disclosed for a series of organometallic reagents.[10] However, catalysts that simultaneously induce high regio- and enantioselection in the arylation of acyclic, unsymmetrical α,γ-disubstituted allylic electrophiles have not been developed.[11] We envisioned that a Ni-catalyzed asymmetric reductive cross-coupling could provide a mild and selective alternative approach to such products. Here, we report a highly enantioselective Ni-catalyzed reductive cross-coupling between vinyl bromides and benzyl chlorides (Figure 1b).[12,13] A variety of alkenyl products

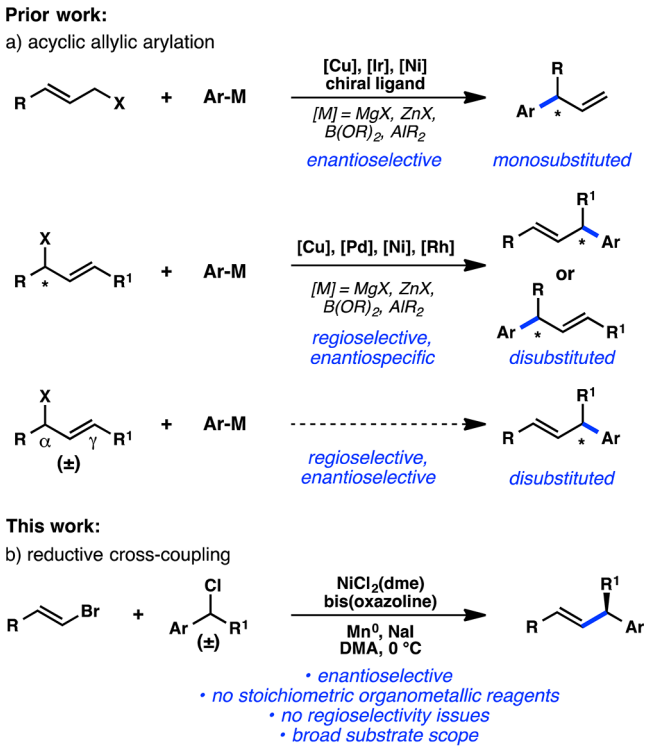

Figure 1. Catalytic asymmetric synthesis of alkenes bearing aryl-substituted allylic stereogenic centers.

bearing allylic stereogenic centers are prepared in good yields with high enantiomeric excess under mild conditions.

Our investigations commenced with the coupling of an equimolar mixture of vinyl bromide **1a** and benzyl chloride **2a** using $NiCl_2$(dme) (10 mol %), a chiral ligand (11 mol %), Mn^0 as the stoichiometric reductant, and DMA as solvent. Several isopropylidene-linked bis(oxazoline) ligands delivered product **3a** in moderate yield and enantioselectivity but favored formation of butane-2,3-diyldibenzene (**4**), arising from homocoupling of **2a** (Table 1, entries 1−3).[14] In all cases, **4** was observed as a 1:1 mixture of the *meso* and *rac* diastereomers. Formation of unreactive chlorostyrene side products, resulting from Ni-catalyzed halide exchange of **1a**, was also observed.[15] Indanyl-substituted ligand **L4** improved the selectivity, permitting formation of **3a** in 26% yield and 70% ee (entry 4). Tuning

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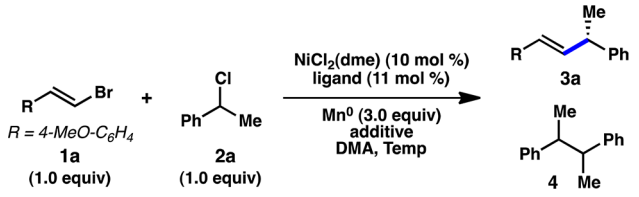
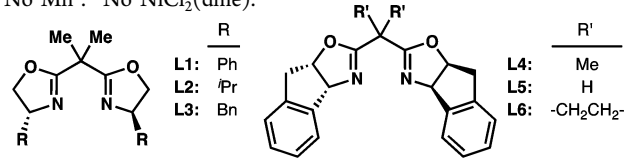
Table 1. Optimization of Ni-Catalyzed Asymmetric Reductive Coupling



entry[a]	ligand	additive	temp (°C)	yield 4 (%)[b]	yield 3a (%)[b]	ee 3a (%)[c]
1	L1	–	20	48	50	40
2	L2	–	20	33	21	57
3	L3	–	20	38	25	68
4	L4	–	20	35	26	70
5	L5	–	20	21	33	49
6	L6	–	20	20	56	87
7	L6	TFA	20	30	39	86
8	L6	TMSCl	20	26	33	73
9	L6	NaI[d]	20	17	67	87
10	L6	TBAI[d]	20	13	64	91
11	L6	NaI[d]	0	8	93	93
12[e]	L6	NaI[d]	0	8	69	89
13[f]	L6	NaI[d]	0	0	0	–
14[g]	L6	NaI[d]	0	0	0	–
15	–	NaI[d]	0	0	0	–

[a]Reactions conducted under N_2 on 0.2 mmol scale for 6 h. [b]Determined by GC vs an internal standard. [c]Determined by SFC using a chiral stationary phase. [d]0.5 equiv. [e]Zn^0 used instead of Mn^0. [f]No Mn^0. [g]No $NiCl_2$(dme).

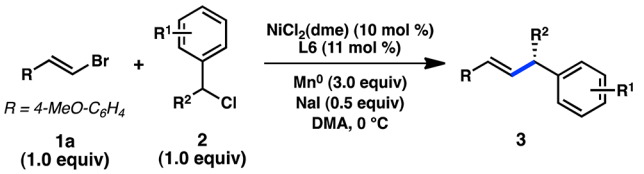


the bite angle of the ligand by changing the central linker revealed that cyclopropyl-linked ligand **L6** produced **3a** in 56% yield and 87% ee (entry 6).

The reaction was further optimized through systematic study of several parameters. Whereas the enantioselectivity was maintained in other polar solvents, increased homocoupling to give **4** was observed; use of ethereal solvents resulted in lower enantioselection.[16] Trifluoroacetic acid (TFA) and trimethylsilyl chloride (TMSCl), additives known to activate the Mn^0 surface, failed to increase reaction efficiency (entries 7 and 8). In contrast, iodide sources, such as NaI or TBAI, improved the yield of **3a** and decreased the yield of **4** (entries 9–10). NaI is known to enhance reactivity in reductive cross-couplings, possibly through acceleration of electron transfer between Mn and Ni or through in situ formation of organo-iodide electrophiles.[17] Lowering the reaction temperature to 0 °C produced **3a** in 93% yield and 93% ee (entry 11). A series of control experiments confirmed that product was not formed in the absence of Mn^0, Ni^{II} precatalyst, or ligand; significant decomposition of vinyl bromide **1a** was also detected in the absence of ligand (entries 13–15).

With optimized conditions in hand, we investigated the scope of the C(sp^3) coupling partner. A variety of benzyl chlorides can be coupled in high yield and high enantioselectivity (Table 2). Whereas *meta* and *para* substitution is well-tolerated, *ortho* substituents result in lower yield and ee (entry 2–4). Functional groups such as methoxide, fluoride, chloride, bromide, and

Table 2. Substrate Scope of Benzyl Chlorides



entry	R^1	R^2	pdt	yield (%)[a]	ee (%)[b]
1	H	Me	3a	91	93
2	4-Me	Me	3b	82	94
3	3-Me	Me	3c	88	93
4[c]	2-Me	Me	3d	44	85
5	4-OMe	Me	3e	64	93
6	4-F	Me	3f	81	89
7[c]	4-Cl	Me	3g	75	88
8	4-Br	Me	3h	59	90
9[c]	4-OCF_3	Me	3i	84	88
10	H	Et	3j	80	97
11	H	Bn	3k	82	93
12	H	4-pentenyl	3l	68	94
13	H	2-hydroxyethyl	3m	81	96
14[c]	H	2-chloroethyl	3n	60	94

[a]Isolated yield, reactions conducted under N_2 on 0.2 mmol scale for 6 h. [b]Determined by SFC using a chiral stationary phase. [c]Run with 15 mol % $NiCl_2$(dme) and 16 mol % L6.

trifluoromethoxide are tolerated (entries 5–9); however, in some cases increased levels of the butane-2,3-diyldiarene product is observed. For these substrates, improved results are achieved with 15 mol % catalyst loading. We were pleased to find that *β*-substituted benzyl chlorides react with no erosion of ee as compared to the parent substrate **2a** (entries 10–14). Alkenyl substrate **2l**, potentially capable of cyclization under radical conditions, exclusively produced uncyclized product **3l** (entry 12). A substrate bearing a free alcohol can also be coupled in high yield and ee (entry 13).

A broad scope of styrenyl bromides undergo the cross-coupling to furnish product **5** in good yields and enantioselectivities (Table 3). Higher catalyst loadings are sometimes necessary to mitigate formation of **4**. Notably, the pinacol boronate (**5j**) and free phenol (**5k**) functional groups are compatible with the reaction, but substrates possessing an aryl ester or nitrile react poorly.[18] Unfortunately, trisubstituted olefins bearing a methyl group in either the *α* or *β* position of the styrene are slow to react (not shown).[16] The reductive cross-coupling can be extended beyond styrenyl systems; e.g., furan **5l** and diene **5m** are prepared in good yield and high ee (Scheme 1). Nonconjugated vinyl bromides are also suitable reaction partners (**5n–p**), as are cyclic benzylic halides (**3o** and **3p**). A limitation of the existing methodology is that *Z*-vinyl bromides react slowly and undergo isomerization to deliver the *E*-alkene product in low yield (not shown).[16]

A series of experiments were conducted to provide insight about the reaction mechanism. The reaction proceeds cleanly in the presence of the radical inhibitor 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT, as high as 50 mol %).[19] In addition, radical clock substrate **6** was found to couple in good yield, without detection of any cyclized product or isomerization of the olefin geometry (Scheme 2a). Taken together, these two results appear inconsistent with a radical chain mechanism and suggest that if oxidative addition of **6** occurs by a stepwise mechanism, radical recombination is rapid and precludes cyclization.[20,21] The

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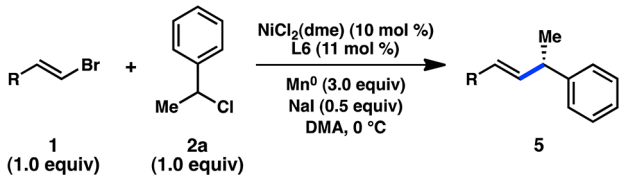
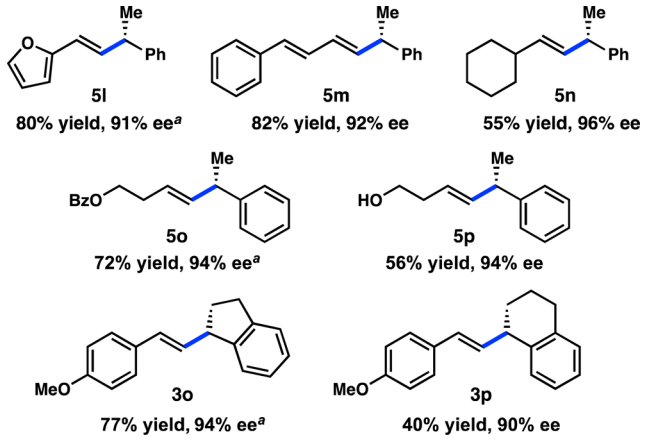
Table 3. Substrate Scope of Styrenyl Bromides



entry	R	pdt	yield (%)[a]	ee (%)[b]
1	4-Me-C_6H_4	5a	83	96
2	4-F-C_6H_4	5b	74	94
3[c]	4-Cl-C_6H_4	5c	66	95
4[c]	4-CF_3-C_6H_4	5d	49	94
5[c]	4-OCF_3-C_6H_4	5e	81	94
6[c]	4-OTBS-C_6H_4	5f	82	96
7[c]	4-NMe_2-C_6H_4	5g	55	95
8[c]	2,3-diMe-C_6H_3	5h	76	96
9[c]	3,4-diMeO-C_6H_3	5i	73	95
10[c]	4-Bpin-C_6H_4	5j	59	94
11	4-OH-C_6H_4	5k	86	93

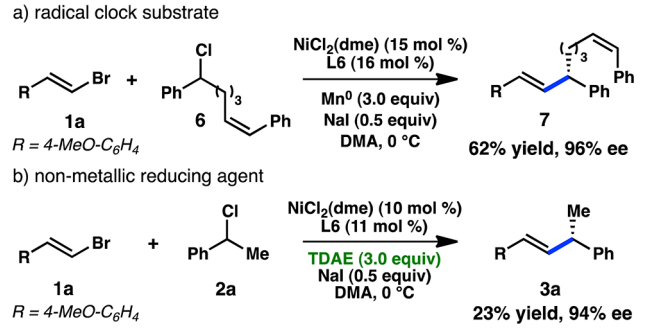
[a]Isolated yield, reactions conducted under N_2 on 0.2 mmol scale for 6 h. [b]Determined by SFC using a chiral stationary phase. [c]Run with 15 mol % $NiCl_2$(dme) and 16 mol % L6.

Scheme 1. Further Investigation of Reaction Scope



[a]Run with 15 mol % $NiCl_2$(dme) and 16 mol % **L6**.

Scheme 2. Mechanistic Investigations



reaction proceeds with the same enantioselectivity when tetrakis(*N*,*N*-dimethylamino)ethylene (TDAE) is employed as the stoichiometric reductant, although the yield is reduced.[22] This finding suggests that cross-coupling of an in situ-generated organomanganese reagent is unlikely. Additional work is required to fully elucidate the reaction mechanism and the origin of enantioinduction.[23]

In conclusion, a highly enantioselective reductive cross-coupling between vinyl bromides and benzyl chlorides has been developed. The reaction occurs under mild conditions and is tolerant of a variety of functional groups, providing products in good yields and high enantioselectivities. This work provides further evidence of the feasibility of developing a broad range of asymmetric reductive cross-coupling reactions, an endeavor that is currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

reisman@caltech.edu

Notes

The authors declare no competing financial interest.

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(18) Yields below 50% were achieved. See SI for details.

(19) In the presence of 10 and 50 mol % BHT, **3a** is obtained in 86% and 76% yield, respectively.

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