

## Enantioselective Alkenylation via Nickel-Catalyzed Cross-Coupling with Organozirconium Reagents

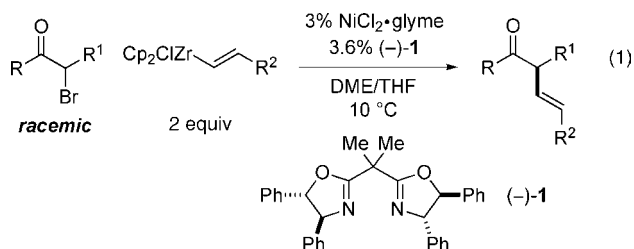
Sha Lou and Gregory C. Fu\*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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Because olefin-containing molecules are ubiquitous targets,<sup>1</sup> the development of effective methods for incorporating this functional group is an important goal. If absolute stereochemistry can also be defined during the bond construction, the utility of a new process is further enhanced. The reaction of secondary alkyl electrophiles with alkenylmetal reagents is an attractive approach to the introduction of olefins, but there are relatively few reports of such cross-couplings.<sup>2,3</sup> Furthermore, there has been only one investigation of an enantioselective variant of this type of process (three examples of cross-couplings of  $\alpha$ -haloesters with alkenyltrimethoxysilanes).<sup>3b</sup>

Alkenylzirconium compounds are appealing alkenylmetals for cross-couplings,<sup>4</sup> in part because they are readily accessible by reacting commercially available Schwartz's reagent ( $\text{Cp}_2\text{ZrHCl}$ ) with alkynes. Although secondary alkyl electrophiles have now been coupled with many different families of organometallic partners (e.g., boron, zinc, magnesium, silicon, tin, and indium compounds),<sup>5</sup> to the best of our knowledge, they have not been cross-coupled with organozirconium reagents.<sup>6</sup> In this report, we describe a mild and versatile method for coupling organozirconium compounds with secondary alkyl halides, specifically, alkenylzirconium reagents with racemic  $\alpha$ -bromoketones; in addition, we establish that this stereoconvergent carbon-carbon bond-forming process can be accomplished with good enantioselectivity to generate potentially labile  $\beta,\gamma$ -unsaturated ketones (eq 1).<sup>7-9</sup>



In initial studies, we attempted to apply previously described methods for nickel-catalyzed asymmetric cross-couplings<sup>8,9</sup> to the alkenylation of 2-bromo-1-phenylpropan-1-one; unfortunately, we did not obtain the desired product in satisfactory yield or ee. We therefore decided to explore the potential utility of a new family of coupling partners, alkenylzirconium reagents. In addition to their ready availability, we anticipated that they could provide another crucial attribute: carbon-carbon bond formation might be achieved under sufficiently mild, nonbasic conditions that racemization of the  $\alpha$  stereocenter and isomerization to the  $\alpha,\beta$ -unsaturated isomer would be avoided. Such complications have thus far precluded a Buchwald-Hartwig-type approach to the catalytic asymmetric alkenylation of carbonyl compounds to generate  $\alpha$  tertiary stereocenters.<sup>10</sup>

We have determined that, under the appropriate conditions, a nickel/bis(oxazoline) catalyst can achieve the stereoconvergent cross-coupling of racemic  $\alpha$ -bromoketones with alkenylzirconium compounds to generate  $\beta,\gamma$ -unsaturated ketones in good yield and ee (Table 1).<sup>11</sup>

**Table 1.** Catalytic Asymmetric Alkenylations with Organozirconium Reagents: Scope with Respect to the Nucleophile<sup>a</sup>

entry	R <sup>2</sup>	yield (%) <sup>b</sup>	ee (%)
1	H	92	90
2	<i>n</i> -Bu	92	92
3	CH <sub>2</sub> Ph	91	93
4	Cy	75	81
5 <sup>c</sup>	<i>t</i> -Bu	86	84
6	Ph	89	91
7	CH <sub>2</sub> OTBS	81	90
8	CH <sub>2</sub> CH <sub>2</sub> OTHP	76	95
9		82	93

<sup>a</sup> All data are the average of two experiments. <sup>b</sup> Yield of purified product. <sup>c</sup> Catalyst loading: 10%  $\text{NiCl}_2\cdot\text{glyme}/12\%$  (-)-1.

Carbon-carbon bond formation occurs below ambient temperature (10 °C) and without the need for any additives (e.g., Brønsted bases) that might erode the enantioselectivity. As illustrated in Table 1, a broad array of alkenylzirconium reagents are suitable cross-coupling partners. Thus, the R<sup>2</sup> group can range in steric demand from hydrogen to *tert*-butyl (entries 1–5). Furthermore, functional groups such as aromatic rings, oxygen substituents, and alkenes are compatible with the reaction conditions (entries 3 and 6–9).

We have also examined the scope of this new cross-coupling process with respect to the  $\alpha$ -bromoketone. As illustrated in Table 2, a diverse set of aryl alkyl ketones are suitable electrophiles. A

**Table 2.** Catalytic Asymmetric Alkenylations with Organozirconium Reagents: Scope with Respect to the Aryl Alkyl Ketone (for the Reaction Conditions, See Eq 1)<sup>a</sup>

entry	ketone	R <sup>2</sup>	yield (%) <sup>b</sup>	ee (%)
1		(CH <sub>2</sub> ) <sub>4</sub> Cl	83	92
2		CH <sub>2</sub> CH <sub>2</sub> Cl	95	80
3		<i>i</i> -Bu	81	82
4		CH <sub>2</sub> Ph	89	95
5		(CH <sub>2</sub> ) <sub>3</sub> CN	74	90
6		cyclopropyl	80	92
7		<i>p</i> -anisyl	83	87
8		CH <sub>2</sub> Ph	74	89
9		CH <sub>2</sub> Ph	91	81
10		CH <sub>2</sub> Cy	85	94

<sup>a</sup> All data are the average of two experiments. <sup>b</sup> Yield of purified product.

**Table 3.** Catalytic Asymmetric Alkenylations with Organozirconium Reagents: Scope with Respect to the Dialkyl Ketone (for the Reaction Conditions, See Eq 1)<sup>a</sup>

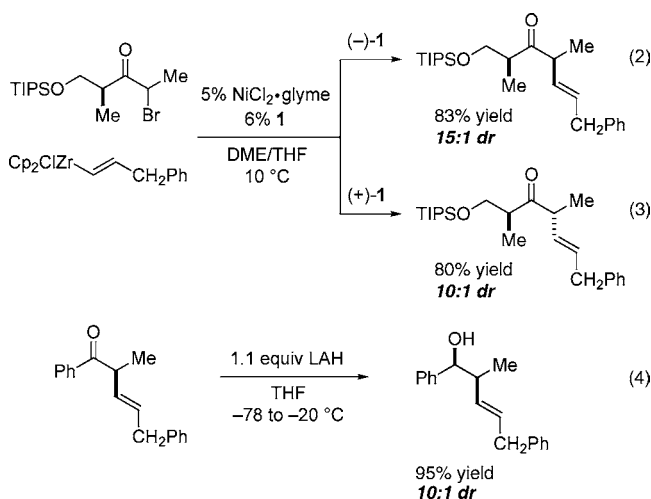
entry	ketone	R <sup>2</sup>	yield (%) <sup>b</sup>	ee (%)
1		CH <sub>2</sub> Ph	86	90
2		CH <sub>2</sub> Ph	82	80
3		CH <sub>2</sub> Ph	82	98
4		CH <sub>2</sub> Ph	87	91
5 <sup>c</sup>		<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	84	90

<sup>a</sup> All data are the average of two experiments. <sup>b</sup> Yield of purified product. <sup>c</sup> The reaction was run at 40 °C.

variety of different types of substituents can be present on the aromatic ring (electron-donating or electron-withdrawing: entries 4–7; ortho, meta, or para: entries 4–9), and the aromatic group can be a heterocycle (e.g., a thiophene in entry 10). In addition, an array of alkyl groups on the ketone and R<sup>2</sup> substituents on the alkenylzirconium reagent are tolerated.

The same method can be applied directly to enantioselective cross-couplings of dialkyl ketones with alkenylzirconium reagents (Table 3). This contrasts with our study of asymmetric Kumada reactions of ketones with aryl Grignard reagents, wherein different coupling conditions (ligand and temperature) were necessary for aryl alkyl ketones versus dialkyl ketones.<sup>9c</sup>

The chiral nickel/bis(oxazoline) catalyst can dictate the stereochemical outcome of a cross-coupling of an  $\alpha$ -bromoketone that bears another stereocenter (i.e., catalyst-controlled stereoselectivity; eqs 2 and 3). Furthermore, stereoselective functionalizations of the cross-coupling product can be achieved (eq 4).



In summary, we have demonstrated that a new family of organometallic compounds, organozirconium reagents, can serve as suitable partners in cross-coupling reactions of (activated) secondary alkyl electrophiles. Thus, we have developed the first catalytic method for coupling secondary  $\alpha$ -haloketones with alkenylmetal reagents, specifically, a mild, versatile, and stereoconvergent carbon–carbon bond-forming process that generates potentially labile  $\beta,\gamma$ -unsaturated ketones with good enantioselectivity. Additional efforts to expand the scope of cross-couplings of alkyl electrophiles are underway.

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**Supporting Information Available:** Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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  - (7) For a catalytic asymmetric method for the  $\alpha$ -alkenylation of aldehydes to generate tertiary stereocenters, see: Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398–399.
  - (8) For an overview and leading references to asymmetric cross-couplings of secondary alkyl halides, see: Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8347–8349.
  - (9) For recent work on asymmetric cross-couplings of secondary alkyl halides, see: (a) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645–12647. (b) Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 154–156. (c) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266.
  - (10) For a discussion and leading references to catalytic asymmetric alkenylations of enolates to generate quaternary stereocenters, see: Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900–9901.
- (11) Notes: (a) In the absence of  $\text{NiCl}_2 \cdot \text{glyme}$  or ligand **1**, the desired product is generated in <5% yield.  $\text{NiBr}_2 \cdot \text{glyme}$  or  $\text{Ni}(\text{cod})_2$  may be used in place of  $\text{NiCl}_2 \cdot \text{glyme}$ . (b) For the cross-coupling illustrated in entry 3 of Table 1: a reaction on a gram scale proceeded at room temperature in 90% yield and 92% ee; use of 1.1, rather than 2, equiv of the organozirconium reagent led to a slower reaction (after 3 days at room temperature: 85% yield, 91% ee). (c) During the cross-coupling, no kinetic resolution of the starting material (the racemic secondary alkyl bromide) is detected, and the ee of the product is constant. (d) After a competition experiment with an  $\alpha$ -bromoketone, an unactivated secondary alkyl bromide was recovered in essentially quantitative yield. (e) In preliminary studies under our standard conditions, an  $\alpha$ -chloroketone, a cyclic  $\alpha$ -bromoketone, and an alkenylzirconium reagent derived from hydrozirconation of an internal alkyne were not suitable cross-coupling partners. (f) The rate law for the cross-coupling is first-order in the catalyst and in the nucleophile, and it is zero-order in the electrophile (NMR studies in *d*<sub>8</sub>-THF).

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