Communication

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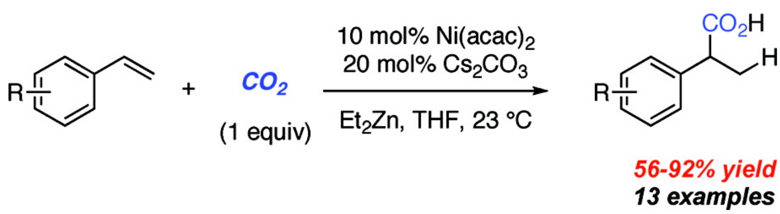

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Nickel-Catalyzed Reductive Carboxylation of Styrenes Using CO_2

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Carbon dioxide is an extremely attractive carbon source that is readily available, inexpensive, and inherently renewable. Its utilization as a C1 feedstock in both large-scale fixation processes and small-scale synthesis has seen considerable growth in recent years.[1] While transition metals promise a mild and efficient alternative for the incorporation of carbon dioxide into organic molecules, such methodology remains largely undeveloped.[2] Current methods for catalyzed carbon−carbon bond formation using CO_2 have been largely limited to reactions with extensive π systems (dienes and diynes)[3,4] or in carboxylation of preformed organometallics.[5] Herein we report a nickel-catalyzed reductive carboxylation of styrenes under an atmosphere of CO_2.

The nickel-mediated stoichiometric fixation of carbon dioxide with alkenes has been known for over 20 years largely due to the work of Hoberg.[6] Inspired by this body of work, we have previously demonstrated that metalacycles such as **2**, generated from cyclic anhydrides and nickel complexes, could be trapped with Ph_2Zn as a nucleophile.[7] We speculated that the use of Et_2Zn could lead to either alkylative (**4**) or reductive (**6**) carboxylation of alkenes if conducted under a CO_2 atmosphere (Scheme 1). Although eminently reasonable on paper, potential problems included balancing desired reactivity with the potential catalyzed direct addition of the alkylzinc reagent to CO_2, as demonstrated recently by others.[5f,g] We were confident, however, that judicious choice of ligand would lead to a favorable outcome.

Initial attempts at the reductive carboxylation of activated styrenes began with electron deficient methyl-4-vinylbenzoate (**7a**). Much to our delight a ligand screen (Table 1, entry 3) revealed that the use of $Ni(COD)_2$, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)[6,4] and Et_2Zn, under CO_2 results in the formation of carboxylic acid **8a** as a single regioisomer in 85% yield. Perhaps most importantly, this α-carboxylated product is generated under 1 atm of CO_2 supplied by a balloon, avoiding specialized gas manipulation.

While the reaction with activated styrene **7a** is quite efficient, the use of styrene itself under identical conditions results in no carboxylated product (Table 1, entry 6).

To expand the utility of the reaction, a series of nitrogen and phosphorus ligands were examined with nearly uniform failure.[8] The success of DBU as a ligand was difficult to rationalize but we speculated that it could be a function of its basicity rather than simply its donor character. That thought led us to investigate bases not typically considered ligands on late transition metals. Basic additives proved moderately successful (Table 1, entry 7), leading us toward examination of a series of inorganic bases as well. The use of Cs_2CO_3 as a ligand/additive affords **8b** in 56% yield (entry 8), and with this result we began exploration of the scope.

Hammett $\sigma_{m/p}$ and σ_p^+ values have proven useful in the prediction of reactivity.[9] With few exceptions, electron deficient styrenes with positive σ values undergo reductive carboxylation very efficiently regardless of substitution pattern (Table 2, 7h, 7k, 7l), while those with negative σ values generally fail to produce the desired product.

Scheme 1. Envisioned Reactivity

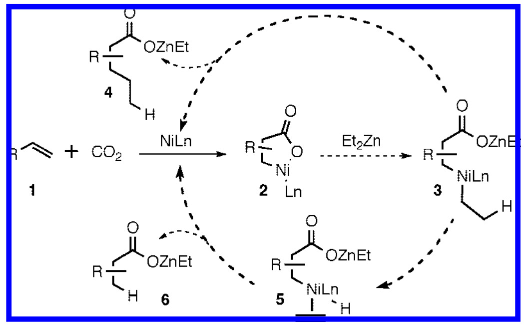
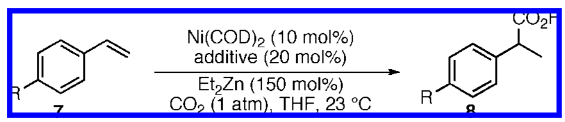
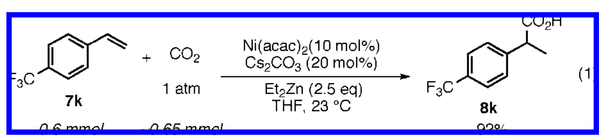


Table 1. Initial Ligand Screen for Reductive Carboxylation



entry	R	additive	yield (%)
1	CO_2Me (a)	none	<5
2	CO_2Me (a)	bipy	NR
3	CO_2Me (a)	DBU	88
4	CO_2Me (a)	pyridine	90
5	CO_2Me (a)	PPh_3	NR
6	H (b)	DBU	NR
7	H (b)	KHMDS	35
8	H (b)	CS_2CO_3	56

Furthermore, the reaction is tolerant of a variety of functional groups, including aryl chlorides, esters, ketones, and nitriles.



Although our screens involve 10 mol % nickel, we have shown that 1 mol % $Ni(acac)_2$ works equally well.[10] Typical reaction conditions utilize a balloon containing approximately 1 L of CO_2 (45 mmol). To test consumption efficiency, a reaction was run in a 15 mL flask with only a headspace of CO_2: roughly 1 equiv of carbon dioxide relative to styrene **7k** (eq 1). Complete consumption of styrene was observed and 92% of **8k** was isolated indicating that the hydrocarboxylation reaction proceeds under CO_2 pressure well below 1 atm.

Although Hoberg's work involving metalacycles provided the intellectual impetus for this research, initial investigations suggest a different mechanism may be operative, one proceeding through a nickel-hydride active catalyst (**B**, Scheme 2). Insertion of styrene into the nickel-hydride bond provides benzyl nickel species **C**; a transmetalation generates the benzylic zinc species **D**, the product

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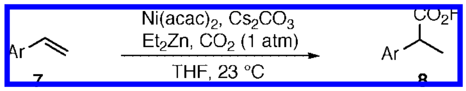
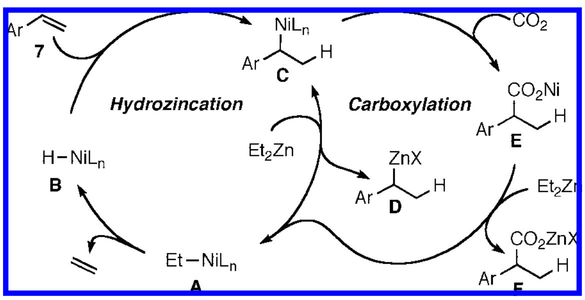
Table 2. Reductive Carboxylation Substrate Scope



entry[a]	Aryl Group (Ar)		$\sigma_{m/p}/\sigma_{+}$[b]	yield (%)[c]
1		**b**	0	56
2		**c**	-	60
3	MeO_2C (O)	**d**	-	66
4	MeO	**e**	0.12	92
5	Cl	**f**	0.37	68
6	Cl	**g**	-	65
7	F_3C	**h**	0.43	79
8	MeO_2C	**a**	0.45/0.48	84
9	BnO_2C	**i**	0.45/0.48	81
10	PhOC	**j**	0.50/0.51	72
11	F_3C	**k**	0.54/0.61	92
12	CF_3	**l**	-	87
13	NC	**m**	0.66/0.66	61

[a] Standard conditions: $Ni(acac)_2$ (10 mol %), Cs_2CO_3 (20 mol %), Et_2Zn (250 mol %). [b] See reference 9. [c] Isolated yield.

Scheme 2. Proposed Reductive Carboxylation Mechanism



of net hydrozincation of the alkene,[11] while also regenerating Et-Ni complex **A**. β-Hydride elimination and release of ethylene from **A** generates the presumed active catalyst **B**.[12] A separate catalytic cycle involving transmetalation back to nickel (**D** to **C**) generates another benzylic nickel species which undergoes insertion of CO_2 prior to transmetalation with Et_2Zn, producing the hydrocarboxylation product **F** and regenerating precatalyst **A**. In support of this mechanism, we note that a D_2O quench after 1 h provides significant amounts of the reduced alkene bearing a deuterium in the benzylic position, suggestive of the presence of **D**.[13,14] Importantly, the direct addition of dialkylzinc reagent to CO_2[5f,g] is extremely slow.[15]

A catalyzed hydrocarboxylation has been developed for a variety of electron deficient and neutral ortho, meta, and para styrene analogues.[16] This reaction represents the foundation of a methodology to incorporate carbon dioxide in the preparation of more complex synthetic intermediates. Of additional interest is the efficient uptake of CO_2, which occurs under only 1 atm of CO_2. Studies to extend the reaction scope[17] are in progress.

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Supporting Information Available: Experimental procedures, ligand screen, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Reaction of **7k** (0.6 mmol) provides **8k** in 89% yield. This also demonstrates Cs_2CO_3 does not provide appreciable amounts of CO_2.
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(12) The use of other reductants (*i*-PrOH, Ph_3SiH, H_2) provides $<10\%$ yield. Me_2Zn does not provide alkylated product; Ph_2Zn affords benzoic acid.
(13) Substrate **7c** provides $>50\%$ ethylnaphthalene with $\sim10\%$ **8c** when quenched after 1 h.
(14) Heterogeneous catalysis remains a consideration, although a preliminary mercury drop experiment does not support it. See:Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A* **2003**, *198*, 317.
(15) A preformed naphthyl methylzinc reagent does not undergo carboxylation in the absence of nickel (18 h, THF, 23 °C, 1 atm CO_2).
(16) For hydroacylation of styrenes using anhydrides and H_2, see:Hong, Y.-T.; Barchuk, A.; Krische, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6885.
(17) Under these conditions, cyclohexadiene, decene, and β-methylstyrene give $<10\%$ yield of expected product.

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