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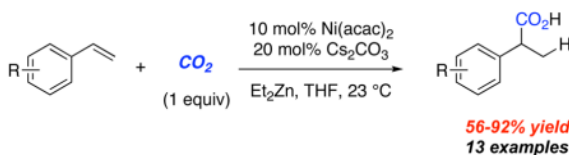
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Nickel-Catalyzed Reductive Carboxylation of Styrenes Using CO₂

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Abstract



A nickel catalyzed reductive carboxylation of styrenes using CO₂ has been developed. The reaction proceeds under mild conditions using diethylzinc as the reductant. Preliminary data suggests the mechanism involves two discrete nickel-mediated catalytic cycles, the first involving a catalyzed hydrozincation of the alkene followed by a second, slower nickel-catalyzed carboxylation of the in situ formed organozinc reagent. Importantly, the catalyst system is very robust and will fixate CO₂ in good yield even if exposed to only an equimolar amount introduced into the headspace above the reaction.

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 CO₂ 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 CO₂.

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 Ph₂Zn as a nucleophile.⁷ We speculated that the use of Et₂Zn could lead to either alkylative (**4**) or reductive (**6**) carboxylation of alkenes if conducted under a CO₂ 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 CO₂, as demonstrated recently by others.^{5f,5g} 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 Et₂Zn, under CO₂ results in the formation of carboxylic acid **8a** as a single regioisomer in 85% yield.

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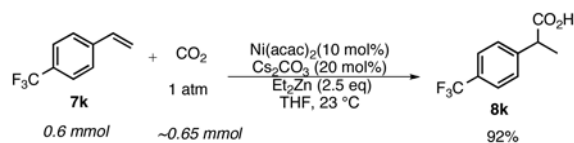
 Supporting Information Available: Experimental procedures, ligand screen and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Perhaps most importantly, this alpha-carboxylated product is generated under 1 atm of CO₂ 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).

In an effort 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 Cs₂CO₃ 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, 8a, 13a, 14a), while those with negative σ values generally fail to produce the desired product. Furthermore, the reaction is tolerant of a variety of functional groups, including aryl chlorides, esters, ketones, and nitriles.



(1)

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 CO₂ (45 mmol). To test consumption efficiency, a reaction was run in a 15 mL flask with only a headspace of CO₂: roughly one equivalent 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 CO₂ 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 of net hydrozincation of the alkene,¹¹ while also regenerating Et-Ni complex **A**. Beta-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 CO₂ prior to transmetalation with Et₂Zn, producing the hydrocarboxylation product **F** and regenerating precatalyst **A**. In support of this mechanism, we note that a D₂O 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 CO₂^{5f,5g} 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 CO₂, which occurs under only 1 atm of CO₂. Studies to extend the reaction scope¹⁷ are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

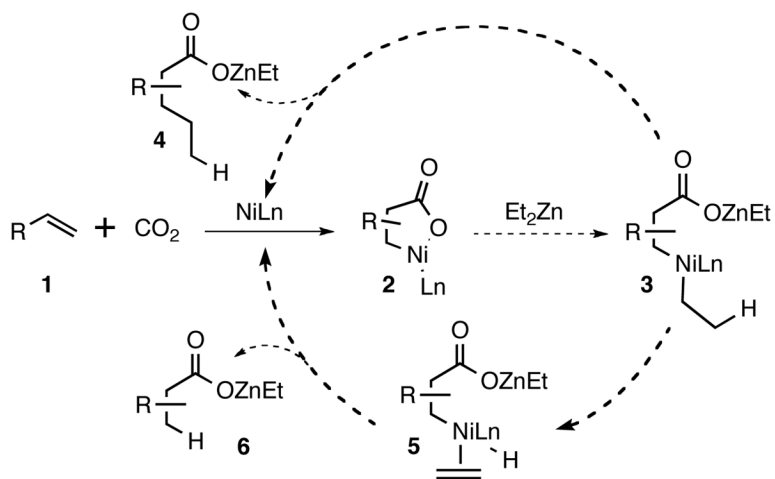
Acknowledgments

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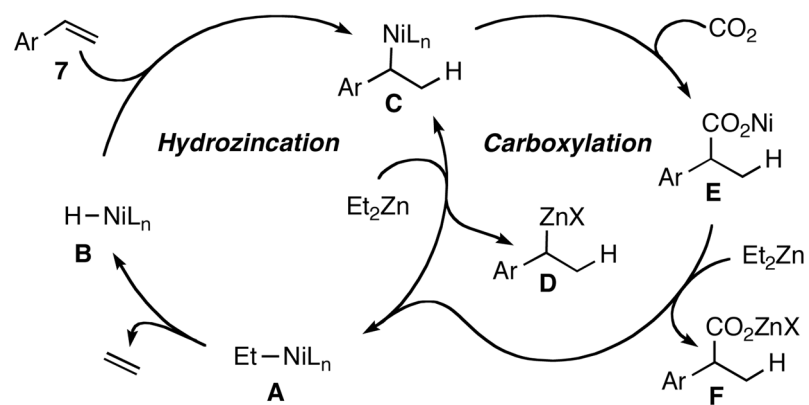
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8. See Supplementary Information.
9. Hansch C, Leo A, Taft RW. *Chem Rev* 1991;91:165.
10. Reaction of **7k** (0.6 mmol) provides **8k** in 89% yield. This also demonstrates Cs₂CO₃ does not provide appreciable amounts of CO₂.
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12. The use of other reductants (*i*-PrOH, Ph₃SiH, H₂) provides <10% yield. Me₂Zn does not provide alkylated product; Ph₂Zn affords benzoic acid.
13. Substrate **7c** provides >50% ethylnaphthalene with ~10% **8c** when quenched after 1 h.
14. Heterogeneous catalysis remains a consideration, although a preliminary mercury drop experiment does not support it. See: Widegren JA, Finke RG. *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 CO₂).
16. For hydroacylation of styrenes using anhydrides and H₂, see: Hong YT, Barchuk A, Krische MJ. *Angew Chem Int Edit* 2006;128:6885.
17. Under these conditions, cyclohexadiene, decene and β-methylstyrene give <10% yield of expected product.



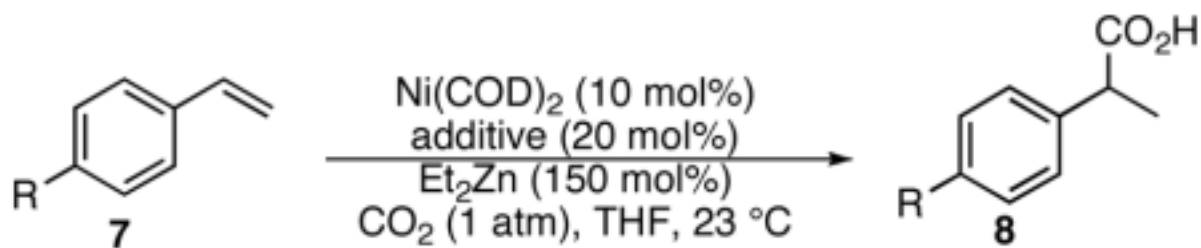
Scheme 1.
Envisioned Reactivity



Scheme 2.
Proposed reductive carboxylation mechanism

Table 1

Initial ligand screen for reductive carboxylation

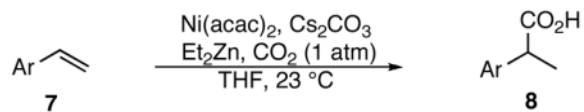


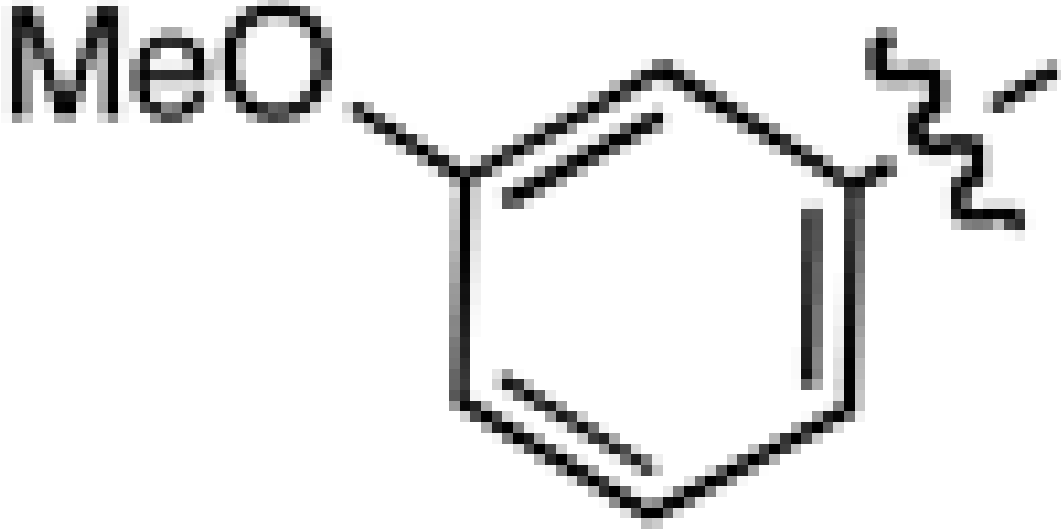
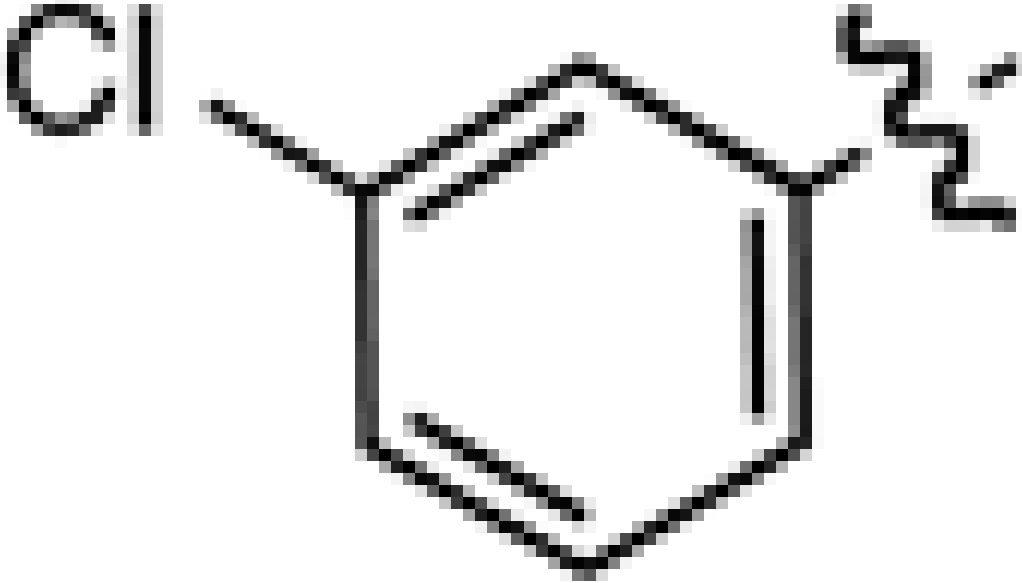
| entry | R | additive | yield (%) |
|-------|------------------------|---------------------------------|-----------|
| 1 | CO ₂ Me (a) | none | <5 |
| 2 | CO ₂ Me (a) | bipy | NR |
| 3 | CO ₂ Me (a) | DBU | 88 |
| 4 | CO ₂ Me (a) | pyridine | 90 |
| 5 | CO ₂ Me (a) | PPh ₃ | NR |
| 6 | H (b) | DBU | NR |
| 7 | H (b) | KHMDS | 35 |
| 8 | H (b) | Cs ₂ CO ₃ | 56 |

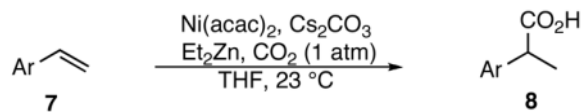
Table 2

Reductive carboxylation substrate scope.

| entry ^a | Aryl Group (Ar) | $\sigma_{m/p}/\sigma_{+}$ ^b |
|--------------------|-----------------|--|
| 1 | b | 0 |
| 2 | c | - |
| 3 | d | - |



| entry ^a | Aryl Group (Ar) | $\sigma_{m/p}/\sigma_+$ ^b |
|--------------------|---|--------------------------------------|
| 4 |  <p style="text-align: center;">e</p> | 0.12 |
| 5 |  <p style="text-align: center;">f</p> | 0.37 |

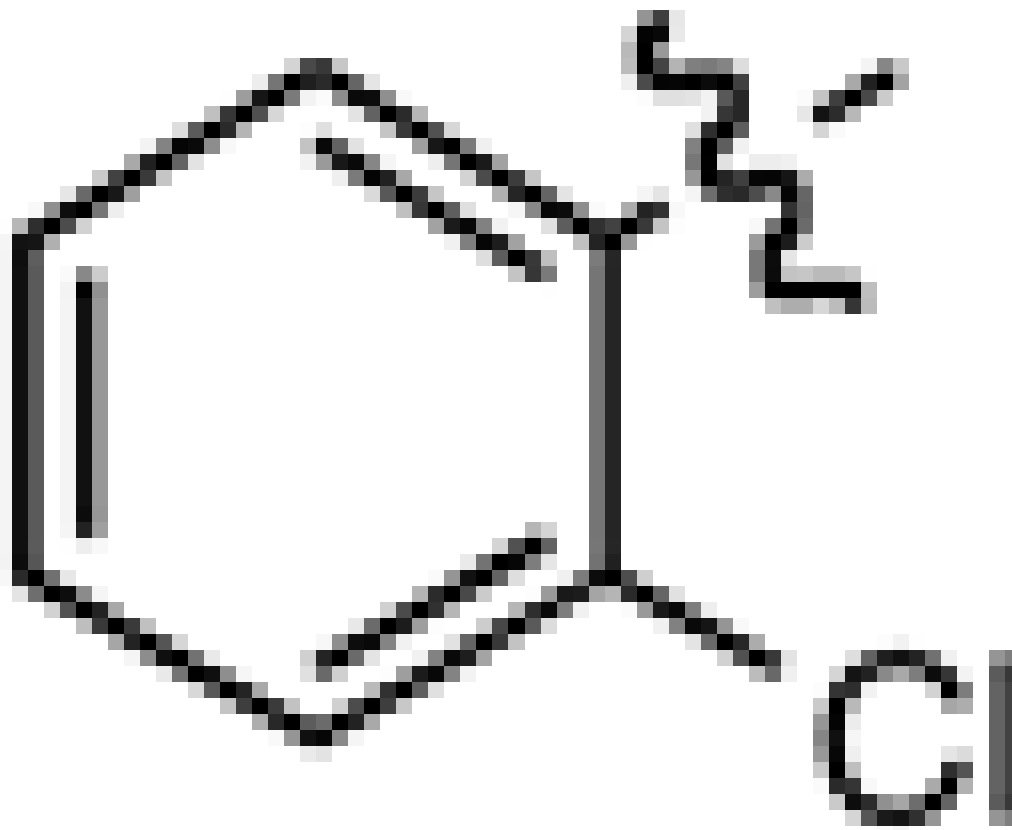
entry^a

Aryl Group (Ar)

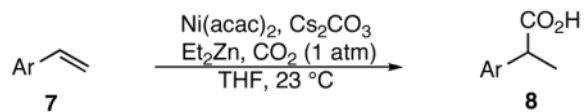
 $\sigma_{\text{m/p}}/\sigma_{\text{+}}$ ^b

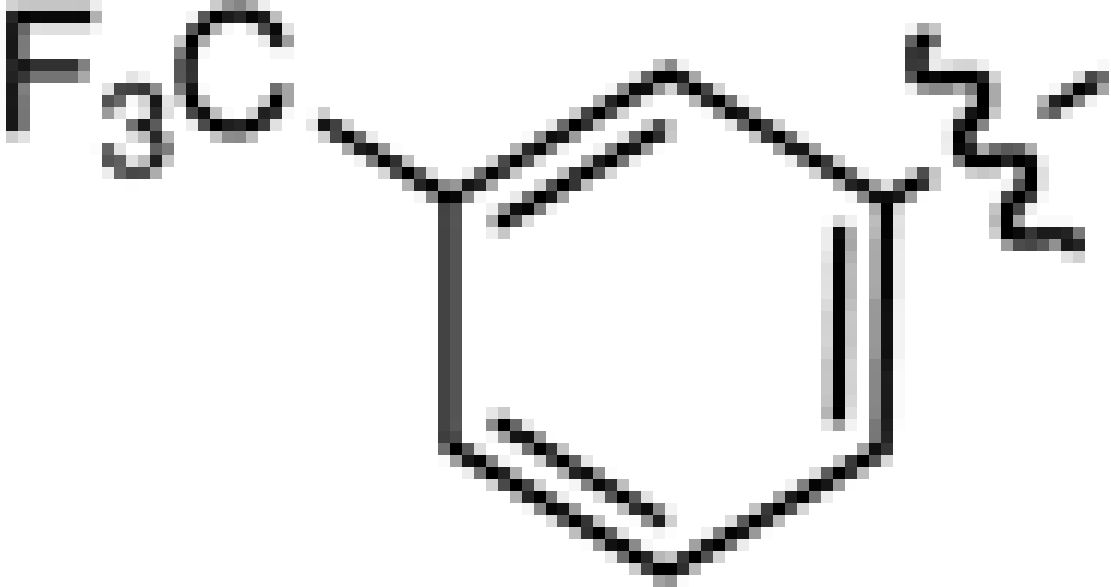
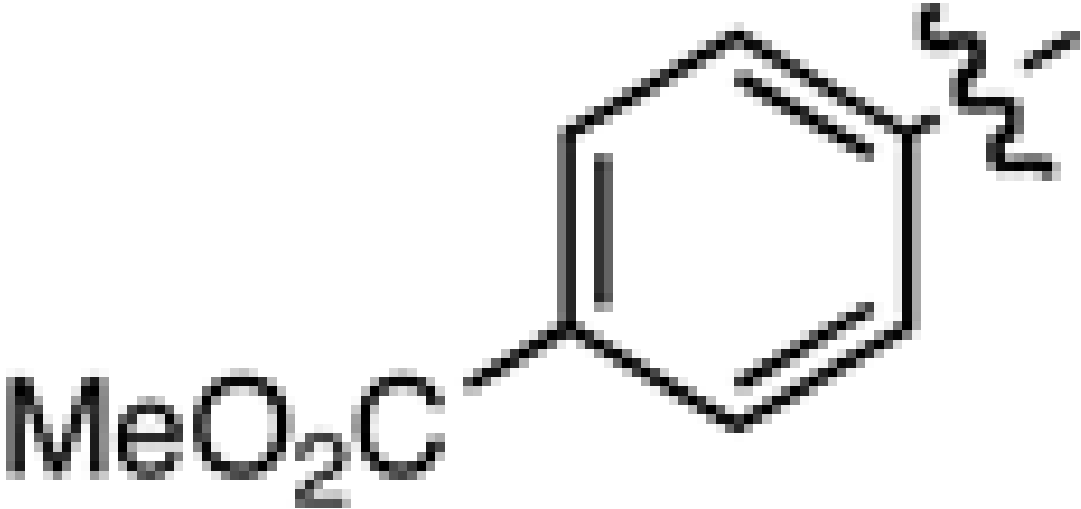
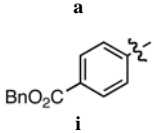
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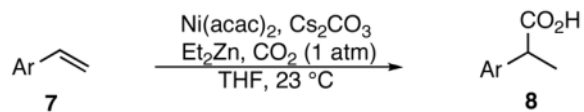
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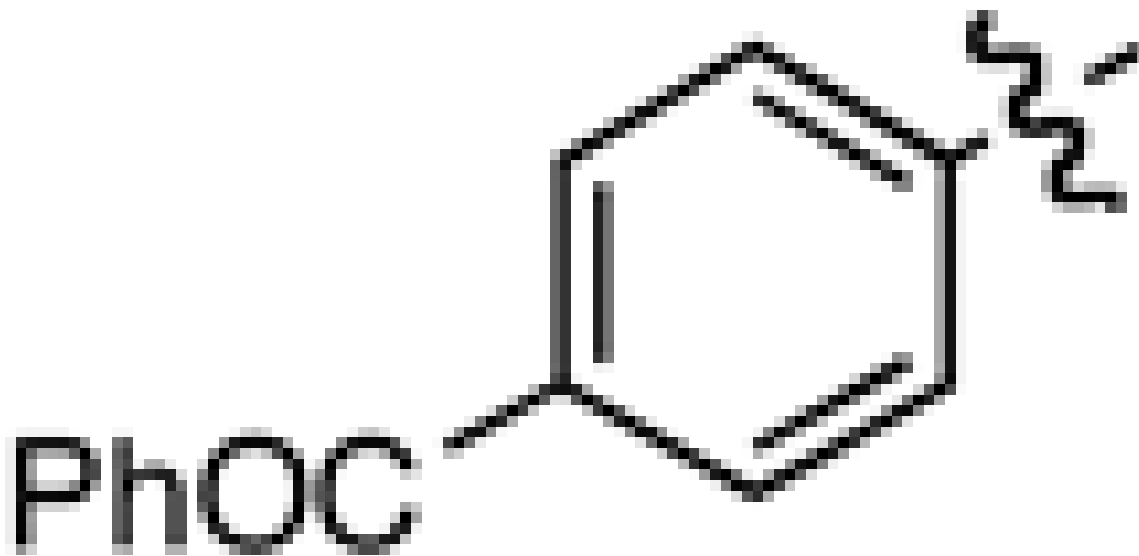
8



| entry ^a | Aryl Group (Ar) | $\sigma_{m/p}/\sigma_+$ ^b |
|--------------------|--|--------------------------------------|
| 7 |  | 0.43 |
| 8 |  | 0.45/0.48 |
| 9 |  | 0.45/0.48 |

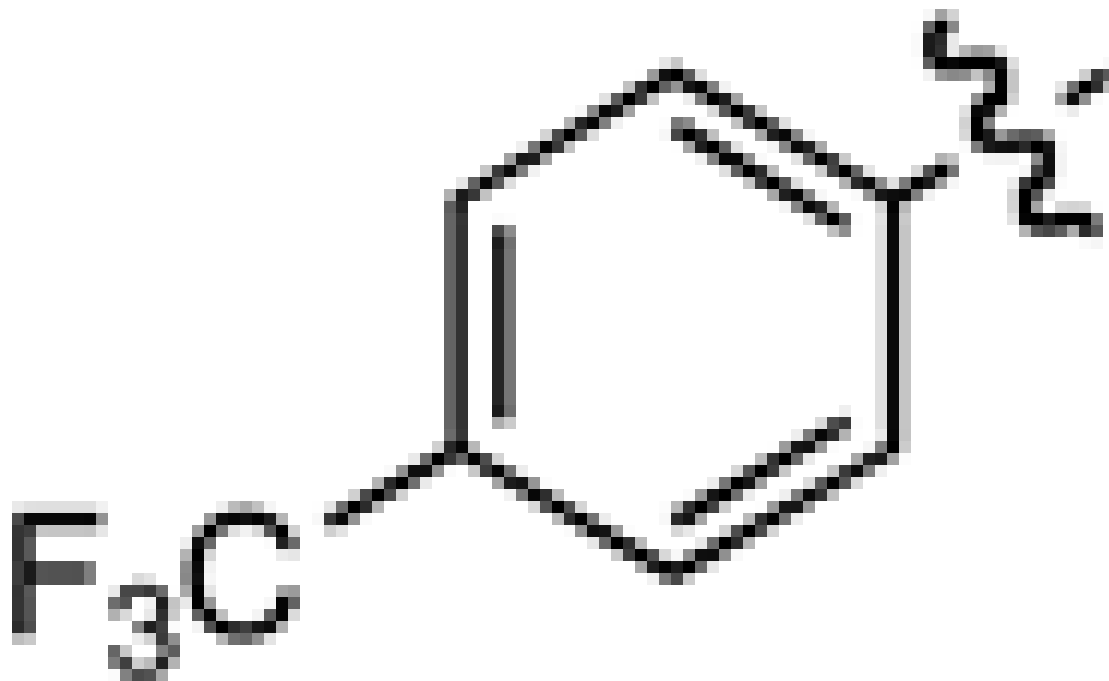


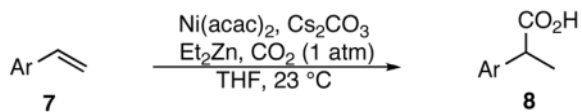
| entry ^a | Aryl Group (Ar) | $\sigma_{m/p}/\sigma_+$ ^b |
|--------------------|-----------------|--------------------------------------|
| 10 | | 0.50/0.51 |



11

0.54/0.61





| entry ^a | Aryl Group (Ar) | $\sigma_{m/p}/\sigma_+$ ^b |
|--------------------|-----------------|--------------------------------------|
| 12 | | - |
| 13 | | 0.66/0.66 |

^aStandard conditions: Ni(acac)₂ (10 mol%), Cs₂CO₃ (20 mol%), Et₂Zn (250 mol%), 18 h.

^bSee reference ⁹.

^cisolated yield.