

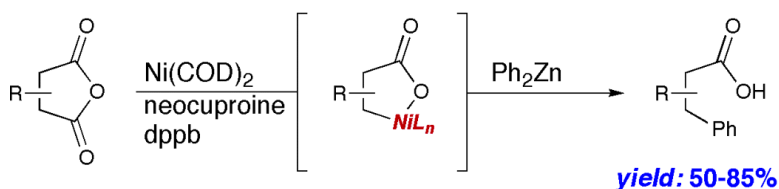
Communication

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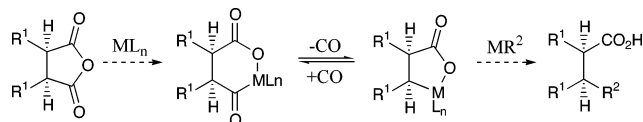
Decarbonylative Cross-Coupling of Cyclic Anhydrides: Introducing Stereochemistry at an sp^3 Carbon in the Cross-Coupling Event

Erin M. O'Brien, Eric A. Bercot, and Tomislav Rovis*

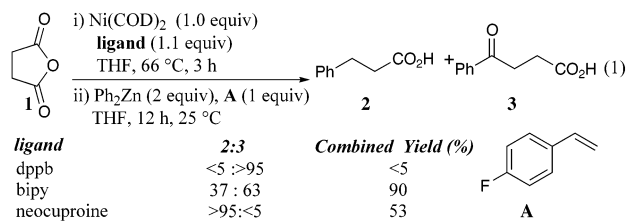
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Metal-catalyzed cross-coupling has been established as a convenient, practical and effective method for the formation of a myriad of sp^2 – sp^2 bonds under mild conditions.¹ Of this stable of name reactions, several are capable of coupling sp^2 electrophiles with sp^3 nucleophiles.² The reverse, coupling sp^3 electrophiles with sp^2 or sp^3 nucleophiles, has seen some remarkable advances in recent years, helping dispel the myth that β -hydride elimination would be an insurmountable problem.³ However, in almost every case, the two sp^3 carbon atoms involved in the cross-coupling are terminal (primary), and stereochemistry is not generated in the cross-coupling event.^{4–6} We report herein a nickel-mediated decarbonylative cross-coupling of meso anhydrides, which constitutes the first example of an sp^3 (electrophile)– sp^2 (nucleophile) cross-coupling reaction that generates stereochemistry.



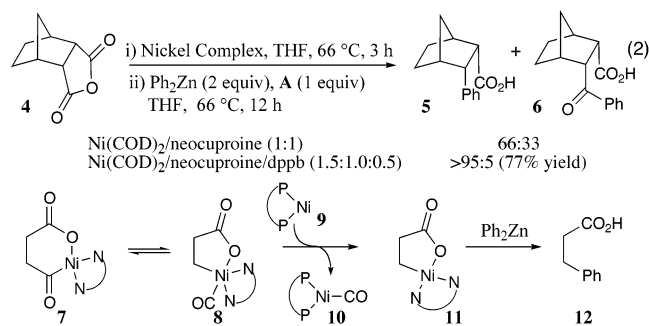
Investigations began with the known insertion of low-valent nickel complexes into cyclic anhydrides.⁷ Decarbonylation⁸ of the initial insertion product provides a nickelalactone possessing a secondary $C(sp^3)$ –Ni bond. We envisioned that this intermediate could be trapped by cross-coupling with an organometallic nucleophile. Organozinc reagents were chosen as nucleophiles on the basis of our previous report.⁹ Anhydride **1** was subjected to a variety of nickel–ligand complexes at 66 °C in THF, in an attempt to find conditions that would afford cross-coupled product **2** and avoid the formation of direct addition product **3**.¹⁰



The reaction is very sensitive to nickel complex, eq 1. Phosphine ligands such as bis(diphenylphosphino)butane (dppb) were not suitable in this reaction and yielded only trace amounts of either product. Although bipyridyl-type ligands provided a mixture of **2** and **3**, increased steric congestion around the metal induced by 2,9-dimethyl-1,10-phenanthroline (neocuproine) resulted in a remarkable increase in decarbonylation efficiency.

Unfortunately, more complex anhydrides still yielded minor amounts of direct addition product, eq 2. We hypothesized that upon decarbonylation, CO remains coordinated to the nickel,¹¹ and may reinsert into the metallacycle, yielding direct addition product. To remove the CO from the nickel–neocuproine complex, we

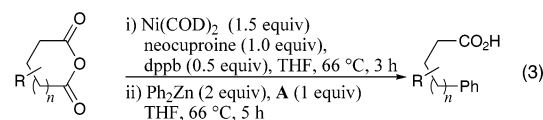
anticipated that the addition of a second nickel–ligand complex with a much greater affinity for CO (more electron-rich) may sequester the byproduct. Given its demonstrated inefficiency at mediating the decarbonylative cross-coupling, dppb seemed the logical choice. This proved successful, completely suppressing the direct addition pathway, eq 2.¹²



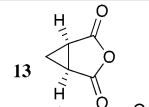
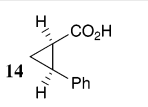
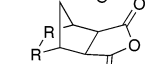
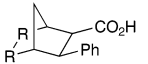
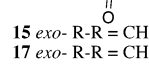
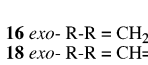
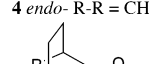
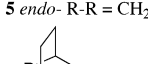
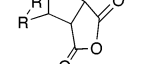
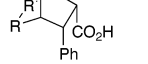
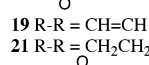
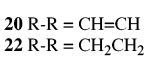
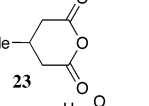
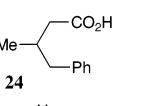
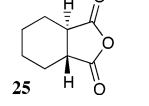
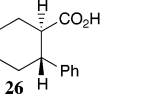
A variety of cyclic anhydrides undergo successful decarbonylative cross-coupling, Table 1. The cyclopropane succinic anhydride **13** provides β -cross-coupled product **14** in 60% yield with no loss of stereochemical integrity. [2.2.1]-Tricyclic anhydride **15** and its two analogues **17** and **4** lead to bicyclic acids, **16**, **18**, and **5** in 78, 56, and 77% yields, respectively. [2.2.2]-Bicyclooctane-derived anhydrides **19** and **21** require higher temperatures for complete decarbonylation, yielding **20** in 51% yield and **22** in 50% yield. Glutaric anhydride **23** affords the desired product in low yield (<20%) when neocuproine is used as a ligand. However, the use of tetramethylethylenediamine (TMEDA, 1.5 equiv) with $Ni(COD)_2$ (2 equiv) and dppb (0.5 equiv) provides γ -cross-coupled product **24** in good yield. *trans*-Cyclohexanedicarboxylic anhydride **25** decarbonylates completely at 45 °C, without any loss of stereochemical integrity to afford a single isomer in 77% yield. The absence of diastereomeric acids in any of these reactions suggests that the integrity of the presumed sp^3 -Ni stereocenter is maintained during the transmetalation/reductive elimination sequence and argues against the possible intervention of alkyl radicals in the cross-coupling.^{13,14}

When succinic anhydride endo-**27** was subjected to these reaction conditions, γ -substituted carboxylic acid **28** was obtained in moderate yield, eq 4. This product presumably arises from alkene insertion into the initially generated nickelalactone **29** to provide new nickelalactone **30**. At this time, it is not clear what drives this reaction; strain energy associated with the five-membered nickelalactone is potentially relieved upon isomerization to the six-membered lactone in **30**, at the expense of the formation of a cyclopropane ring. It is also conceivable that the transmetalation to **30** is faster for steric reasons. This reaction does not occur with exo-**17**, suggesting that the cyclization does not occur from homolytic cleavage of the Ni–C bond.

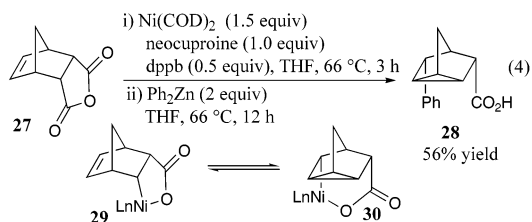
Table 1. Substrate Scope in the Nickel-Mediated Decarbonylative Cross-Coupling of Cyclic Anhydrides



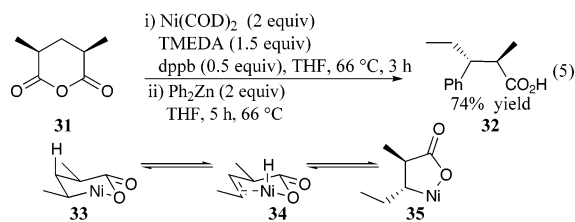
 i) Ni(COD)₂ (1.5 equiv), neocuproine (1.0 equiv), dppb (0.5 equiv), THF, 66 °C, 3 h
 ii) Ph₂Zn (2 equiv), A (1 equiv), THF, 66 °C, 5 h

Entry	Anhydride	Product	Yield (%) ^d
1			60
2			78
3			56
4			77
5			51 ^b
6			50 ^b
7			85 ^c
8			77 ^d

^a Isolated yield of analytically pure material. In every case, direct addition product is not visible by ¹H NMR in the unpurified reaction mixture (<5%). Mass balance typically resides in reduced decarbonylated product. ^b Reaction conducted in dioxane at 80 °C. ^c Reaction conducted using TMEDA (1.5 equiv), Ni(COD)₂ (2 equiv). ^d Reaction conducted at 45 °C.



Subjection of *meso*-dimethyl glutaric anhydride **31**, to the prescribed reaction conditions results in β -cross-coupled product **32**, formed as a single diastereomer in 74% yield, eq 5. This presumably proceeds via isomerization of δ -nickelalactone **33** to γ -nickelalactone **35** by a β -hydride elimination/hydrometalation sequence.¹⁵



In summary, we have developed a nickel-mediated decarbonylation/cross-coupling of *meso* anhydrides, which constitutes the first example of an sp³(electrophile)–sp²(nucleophile) cross-coupling reaction that generates stereochemistry. Efforts to expand the scope and render the system catalytic in nickel are currently under way.

Acknowledgment. We thank Colorado State University, the donors of the Petroleum Research Fund (administered by the American Chemical Society), Merck, and Glaxo-SmithKline for financial support. E.A.B. thanks Pharmacia for a graduate fellowship. We thank Andrew Bolig and Professor Eugene Chen (CSU) for assistance in the preparation of Ph₂Zn.

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

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- (12) In theory, this reaction may be made catalytic in neocuproine–nickel complex when conducted in the presence of 0.5 equiv of Ni–dppb complex. However, under these conditions, the decarbonylated product **5** is formed along with the direct addition product **6** (1:1.5), suggesting that transmetalation to intermediate **7** may be kinetically competitive with decarbonylation/CO-sequestration.
- (13) Alkyl iodides have been used as cross-coupling partners to nickelacycles (see refs 8c–e), but Echavarren has shown that the reaction proceeds via radical intermediates and does not generate stereochemistry; see ref 8c.
- (14) Diarylzinc reagents formed in situ from aryllithium and ZnCl₂ also participate in this reaction; see Supporting Information for details.
- (15) Subjection of glutaric anhydride to these reaction conditions provides 3- and 4-phenylbutanoic acid in a 1:3.75 ratio, and 77% combined yield. Apparently, cross-coupling is preferred at a primary C–Ni bond over a secondary; between two secondary positions, the ring-contracted metalacycle is favored.

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