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Regioselective Cross-Coupling

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Alkene-Directed Regioselective Nickel-Catalyzed Cross-Coupling of Cyclic Anhydrides with Diorganozinc Reagents**

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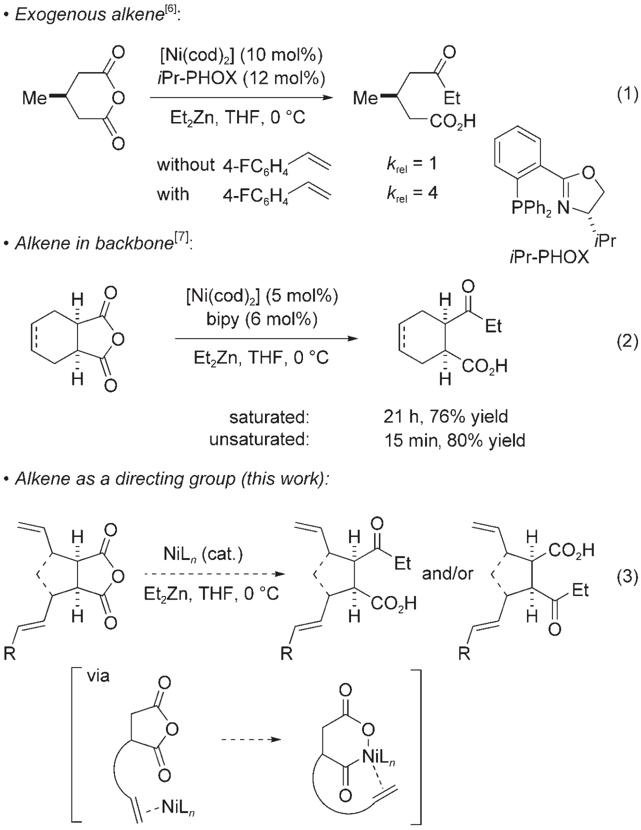
Substrate-directed reactions are a mainstay of organic chemistry. Numerous transformations are susceptible to direction by a resident functional group,[1] with the majority involving the assistance of a Lewis basic group, such as an alcohol, carbonyl, or imine, or a hydrogen-bond donor, such as an alcohol. Examples where olefins provide a directing effect are far fewer, despite alkenes having a greater functional-group tolerance than typical Lewis bases.[2,3] In a seminal report, Marek, Beruben, and Normant showed that a pendant terminal alkene promotes diastereoselective allylzincation of a second alkene.[2a] Krafft, Jamison, and Hoveyda and their co-workers have subsequently documented terminal olefin effects on palladium-catalyzed allylic alkylation,[2b] nickel-catalyzed reductive alkyne aldehyde coupling,[2c] and asymmetric ruthenium-catalyzed ring-opening metathesis/cross-metathesis[2d], respectively. These important early studies have shown that an alkene can direct the outcome of a chemical reaction, but in these studies, the structural features responsible for these effects were not established. In particular, complex systems may have more than one alkene present and it may be necessary to understand the relative ability of olefins, terminal and internal, to direct reactivity in such transformations. Herein we report the nickel-catalyzed regioselective olefin-directed cross-coupling of anhydrides with diorganozinc nucleophiles, and illustrate the relative propensity of several different olefins to direct the alkylation.

We have reported that nickel complexes catalyze the cross-coupling of cyclic anhydrides with diorganozinc reagents.[4] The reaction is accelerated by the addition of styrenic olefins, and follows the precedent of Knochel et al.[5] We have recently determined that the use of an exogenous styrenic additive in catalytic amounts results in a four-fold rate increase, [Eq. (1), Scheme 1].[6] In the absence of these styrenic promoters, significant enhancement of reactivity is observed when the substrate contains an olefin in the backbone [Eq. (2), Scheme 1].[7] This effect is attributed to intramolecular activation of the nickel center through olefin coordination. Mechanistic investigations involving nickel(0)–phosphinooxazoline catalysts reveal a profound dependence on added alkene and point to rate-limiting oxidative addition, a step apparently accelerated by the added olefin.[6]



Scheme 1. Three alkene effects that lead to a directed reaction. cod = 1,5-cyclooctadiene.

To further investigate this effect, we prepared a series of anhydrides to which an olefin promoter is appended. We hypothesized that by tethering an olefin to the anhydride, we could affect regioselective alkylation through olefin-directed nickel insertion and subsequent cross coupling [Eq. (3), Scheme 1]. Successful implementation of this strategy would provide an opportunity to examine the relative directing effect of different olefins, a finding which could have ramifications on synthetic planning involving other metal-catalyzed reactions.

This work takes advantage of extensive studies performed on the ring-opening metathesis/cross metathesis (ROM/CM) of norbornenyl systems, which includes an asymmetric variant.[8] Commercially available *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**1**) undergoes ROM/CM with

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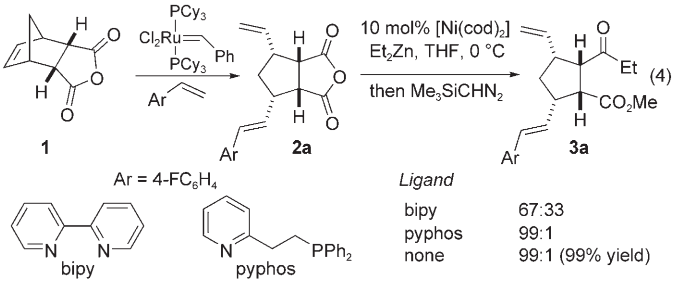
terminal olefins to afford a number of substrates [Eq. (4)]. In this manner, substrates with varying substitution patterns on the disubstituted alkene may be generated, including those bearing silyl, stannyl, ketone, and allyl ether residues.



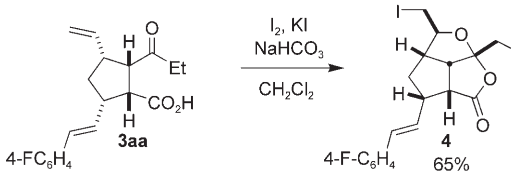
(4)

Ligand	
bipy	67:33
pyphos	99:1
none	99:1 (99% yield)

After screening conditions using **2a**, we found that $[\mathrm{Ni(cod)_2}]$ in the absence of added ligand affords the alkylated product in high yield and excellent regioselectivity. The use of 2-diphenylphosphinoethylpyridine (pyphos) as a ligand gives identical results, while bipyridyl (bipy) results in lower selectivities.[9] The presence of styrene has a modest effect on regioselectivity: the use of 20 mol % as an additive provides slightly reduced 92:8 regioselectivity while five equivalents relative to substrate still affords 90:10 selectivity. The resident olefin appears to largely override the effect of exogenous alkene.

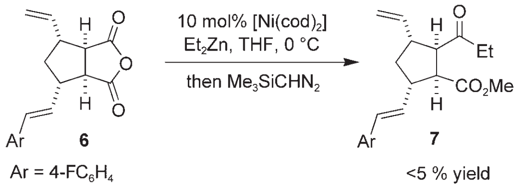
To confirm the identity of the major product, the ketoacid **3aa** derived from **3a** was subjected to iodolactonization [Eq. (5)].[10] An X-ray crystal structure of the product **4** (see the Supporting Information) indicates that alkylation occurs with apparent direction by the terminal olefin. Cyclic anhydrides bearing a variety of different substituents undergo regioselective alkylation in good yields, with good to excellent regioselectivities (Table 1). Of note is the tolerance of the reaction to various substituted olefins, including styrenes, aliphatic alkenes, and allyl stannanes. It appears that steric factors govern selectivity; in all cases alkylation occurs on the side of the terminal alkene.

Other diorganozinc nucleophiles behave analogously. Treatment of anhydride **2a** with Me_2Zn, iPr_2Zn, and Ph_2Zn affords the corresponding alkylated products with high regioselectivity (Table 2). The functionalized zinc homoenolate[11] is also a competent nucleophile, resulting in formation of the desired coupling product in 79 % yield and high selectivity (Table 2, entry 5).



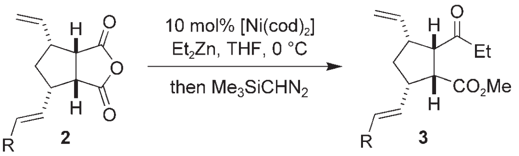
(5)

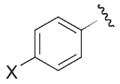
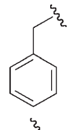
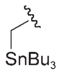
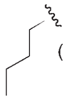
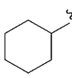
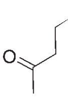
To further test our hypothesis that olefin coordination dictates regioselectivity, we conducted several control experiments. Anhydride **6** was synthesized from the *exo* diastereomer of **1**, having the olefins in a *trans* relationship to the anhydride moiety. Subjection of **6** to the standard alkylation conditions affords less than 5 % yield of the cross-coupled product **7** [Eq. (6)]. This result is in contrast with the high yield and regioselectivity obtained with diastereomeric anhy-



(6)

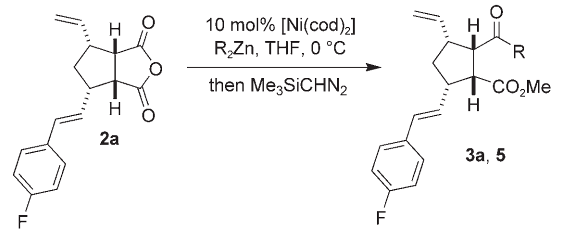
Table 1: Substrate scope in the alkylation of **2** to **3**.



Entry[a]	R	Yield [%]; regioselectivity[b]	Entry[a]	R	Yield [%]; regioselectivity[b]
			7	 (**g**)	95; 98:2
1	X=F (**a**)	99; 99:1			
2	X=H (**b**)	86; 98:2	8	*cis* (**h**)	66; >95:5[c,d]
3	X=OMe (**c**)	96; 95:5[c]	9	*trans* (**i**)	70; >95:5[c,d]
					
4	 (**d**)	99; 98:2	10	*cis* (**j**)	64; 95:5[c]
5	 (**e**)	92; 98:2	11	*trans* (**k**)	68; 85:15[c]
6	 (**f**)	50; 98:2	12	 (**l**)	73; 76:24[c]

[a] All reactions conducted in the presence of $[\mathrm{Ni(cod)_2}]$ (10 mol %) and Et_2Zn (1.7 equiv) at 0 °C in THF for 12 h unless otherwise indicated. TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl. [b] Regioselectivity determined by GC analysis unless otherwise indicated. [c] Regioselectivity determined by ^1H NMR spectroscopy. [d] $[\mathrm{Ni(acac)_2}]$ (10 mol %), Et_2Zn (2.0 equiv) at 0 °C in THF for 30 min.

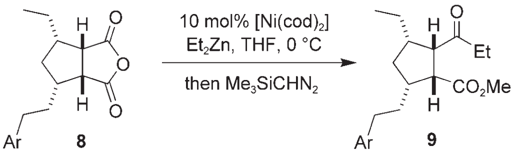
Table 2: Zinc nucleophile scope.



Entry[a]	R	Yield [%]	Regioselectivity[b]
1	Me (**5a**)	94	92:8
2	Et (**3a**)	99	99:1
3	*i*Pr (**5b**)	55	95:5
4	Ph (**5c**)	86	87:13
5	$(CH_2)_2CO_2Et$ (**5d**)	79	90:10[c]

[a]–[c] See footnotes of Table 1.

dride **2a**. We hypothesize that the olefins of **6** are unable to simultaneously ligate the nickel center and direct the insertion into the anhydride, rendering the reaction extremely sluggish. Unlike the parent reaction with nickel and bipy,[6] alkylation of a substrate lacking a resident olefin does not proceed under these conditions [Eq. (7)]. The lack of reactivity of anhydrides **6** and **8** suggests the presence and placement of the olefin are crucial for reactivity.

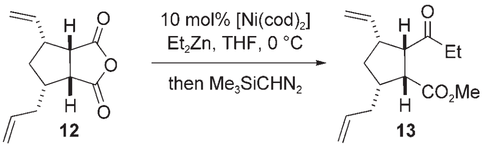


8 **9**

<5 % yield (7)

In the absence of terminal olefins, internal alkenes also direct the alkylation reaction. We subjected various anhydrides from Table 1 to monoreduction conditions[12] to afford **10** (Table 3). Only modest regioselectivities (75:25) are observed in alkylation of anhydrides **10** using conditions optimized for anhydrides **2**. These selectivities are significantly improved with [Ni(acac)$_2$] as a precatalyst (Table 3). Direction now occurs with regiocomplementarity to the parent substrate, **2a**, affording the product of apparent direction by the substituted olefin (Table 3). Successful alkylation of **10e** is particularly interesting, as Tolman has shown that bulky *trans* olefins are among the most weakly binding alkene ligands for nickel(0).[13]

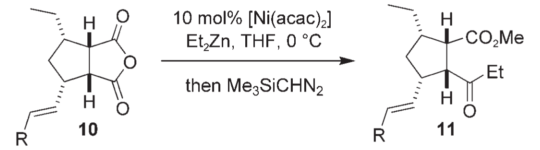
This transformation is also capable of distinguishing between two terminal olefins differentiated by a single methylene spacer. Substrate **12** provides a cross-coupled product consistent with the alkylation event directed by the proximal olefin [Eq. (8)].

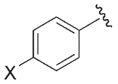
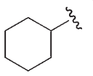
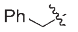
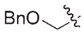


12 **13**

45 % yield, 80:20 (8)

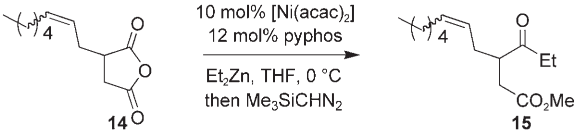
Table 3: Substrate scope of monoreduced anhydrides.



Entry[a]	R	Yield [%]	Regioselectivity[b]
			
1	X=F (**a**)	98	>95:5
2	X=H (**b**)	86	>95:5
3	X=OMe (**c**)	81	>95:5
4	 (**e**)	77	>95:5
5	 (**g**)	92	>95:5
6	 (**m**)	65	86:14

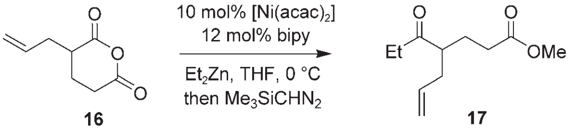
[a] All reactions conducted in the presence of [Ni(acac)$_2$] (10 mol%) and Et$_2$Zn (2.0 equiv) at 0°C in THF for 1 h. Bn = benzyl. [b] Regioselectivity determined by ^{1}H NMR spectroscopy.

Importantly, this methodology is not limited to bicyclic anhydrides, such as **2**. Subjecting commercially available 2-octen-1-ylsuccinic anhydride (**14**) to standard alkylation conditions followed by esterification provides the desired keto ester **15** in quantitative yield and high regioselectivity [Eq. (9)].[14] In addition to succinic anhydrides, the corresponding allylated glutaric anhydrides also undergo a similar directed cross-coupling reaction. Subjecting 2-allylglutaric anhydride (**16**) to the standard reaction conditions provides the ketoester **17** in high yield and high regioselectivity [Eq. (10)].



14 **15**

99 % yield, 90:10 (9)



16 **17**

99 % yield, >95:5 (10)

In summary, we have developed a catalytic regioselective alkylation of asymmetric succinic and glutaric anhydrides directed by resident alkenes, and examined the relative propensity of alkene directing ability. In substrates containing multiple olefins, regioselectivity is apparently determined by the most tightly binding alkene, which is typically the least substituted double bond. In the absence of terminal alkenes, internal olefins are also competent directing groups. Efforts to broaden the scope of this transformation and apply this strategy to other metal-catalyzed reactions are currently underway.

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[1] A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307–1370.

[2] a) Allylzincation: I. Marek, D. Beruben, J.-F. Normant, *Tetrahedron Lett.* **1995**, *36*, 3695–3698; b) Allylic alkylation: M. E. Krafft, M. Sugiura, K. A. Abboud, *J. Am. Chem. Soc.* **2001**, *123*, 9174–9175; c) Reductive coupling: K. M. Miller, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 15342–15343; K. M. Miller, T. Luanphaisarnnont, C. Molinaro, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 4130–4131; R. M. Moslin, K. M. Miller, T. F. Jamison, *Tetrahedron* **2006**, *62*, 7598–7610; d) Metathesis: R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2007**, *129*, 3824–3825.

[3] The presence of olefins also leads to distinct reactivity; for a review encompassing this topic, see: J. B. Johnson, T. Rovis, *Angew. Chem.* **2007**, DOI: 10.1002/ange.200700278; *Angew. Chem. Int. Ed.* **2007**, DOI: 10.1002/anie.200700278.

[4] a) E. A. Bercot, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 174–175; b) E. M. O'Brien, E. A. Bercot, T. Rovis, *J. Am. Chem. Soc.* **2003**, *125*, 10498–10499.

[5] R. Giovannini, T. Studemann, A. Devasagayaraj, G. Dussin, P. Knochel, *J. Org. Chem.* **1999**, *64*, 3544–3553. Also see: E. Shirakawa, Y. Yasuhara, T. Hayashi, *Chem. Lett.* **2006**, *35*, 768–769.

[6] J. B. Johnson, E. A. Bercot, J. M. Rowley, G. W. Coates, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 2718–2725.

[7] E. A. Bercot, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 247–254.

[8] a) J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955; b) J. J. Van Veldhuizen, D. G. Gillingham, S. B. Garber, O. Kataoka, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 12502–12508; c) G. D. Cuny, J. Cao, J. R. Hauske, *Tetrahedron Lett.* **1997**, *38*, 5237–5240; d) M. F. Schneider, N. Lucas, J. Velder, S. Blechert, *Angew. Chem.* **1997**, *109*, 257–259; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 257–259.

[9] [Ni(acac)$_2$] is also an excellent precatalyst, providing ketoacid with 99:1 regioselectivity.

[10] See Supporting Information for details.

[11] M. T. Crimmins, P. G. Nantermet, *J. Org. Chem.* **1990**, *55*, 4235–4237.

[12] J. Tsuji, H. Nagashima, T. Takahashi, K. Masaoka, *Tetrahedron Lett.* **1977**, *18*, 1917–1918.

[13] C. A. Tolman, *J. Am. Chem. Soc.* **1974**, *96*, 2780–2789.

[14] Regioselectivity determined after reduction of olefin.