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Selective Substituent Transfer from Mixed Zinc Reagents in Ni-Catalyzed Anhydride Alkylation

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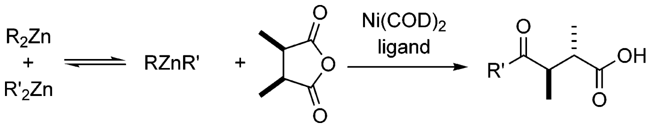
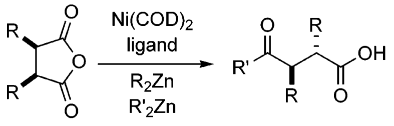
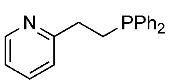
ABSTRACT

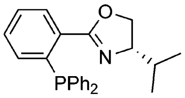


The use of mixed zinc reagents in Ni-catalyzed anhydride alkylation results in preferential transfer of substituents (Ph > Me > Et ≫ *i*Pr ∼ TMSCH$_2$) for the ligands bipy, dppe, and *i*PrPHOX. Utilization of such mixed species allows the use of 0.55 equiv of the diorganozinc reagent, effectively transferring both desired substituents when used in conjunction with a suitable second zinc reagent.

The formation of carbon−carbon bonds through transition-metal-mediated processes has revolutionized organic synthesis.[1] The mild reaction conditions required for these cross-couplings are quite beneficial, as a wide variety of functional groups are tolerated. Although a variety of activated acyl species, including acid chlorides,[2] thioesters,[3] aryl trifluoroacetates,[4] and acyl cyanides,[5] have been applied in the formation of ketones,[6] anhydrides have only recently been investigated as acylating agents in metal-mediated reactions.[7] Goossen[8] and Yamamoto[9] have independently reported the palladium-catalyzed cross-coupling of mixed acyclic anhydrides with boronic acids, whereas Frost has reported a rhodium-catalyzed analogue.[10] Although these reactions provide a powerful means of producing ketones, they inherently lack the ability to influence the formation or definition of stereocenters. Our group has recently reported the development of a similar cross-coupling methodology utilizing cyclic carboxylic anhydrides.[11] Alkylation of such anhydrides with diorganozinc reagents catalyzed by nickel or palladium provides ketoacid derivatives with stereodefined backbones (eq 1).




pyphos (**1**)


*i*PrPHOX (**2**)

The alkylation of a cyclic anhydride with a diorganozinc reagent is efficiently catalyzed by Ni and an appropriate

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(1) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998.

(2) (a) Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (c) Milstein, D.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 1613.

(3) (a) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189. (b) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (c) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033.

(4) Kakino, R.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 371.

(5) Duplais, C.; Bures, F.; Sapountzis, I.; Korn, T. J.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2968.

(6) Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177.

(7) We have recently shown that acid fluorides are also competent cross-coupling partners: Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 15964.

(8) (a) Goossen, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3458. (b) Goossen, L. J.; Ghosh, K. *Eur. J. Org. Chem.* **2002**, 3254.

(9) (a) Kakino, R.; Narahashi, H.; Shimizu, I.; Yamamoto, R. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1333. (b) Kakino, R.; Yasumi, S.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 137. (c) Yamamoto, A. *J. Organomet. Chem.* **2002**, *653*, 5.

(10) Frost, C. G.; Wadsworth, K. J. *Chem. Commun.* **2001**, 2316.

(11) (a) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174. (b) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 10248. (c) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247.

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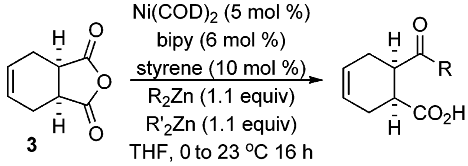
ligand. A limitation of this chemistry, however, is that only one of the two zinc substituents is transferred during reaction. To address this issue, we turned to the chemistry of Knochel and co-workers, who have described the use of mixed zinc reagents.[12] As diorganozinc reagents metathesize at room temperature,[13] a species containing one readily transferred substituent and one slowly transferred substituent can be prepared from the two parent species. Such mixed zinc reagents, through various means of generation, have been utilized for carbonyl additions.[14,15] In several cases, mixed zinc reagents have been used in Cu(I)-mediated conjugate additions.[16,17]

Table 1. Mixed Zinc Alkylation of **3** Catalyzed by Ni(COD)$_2$ and Bipy



(2)

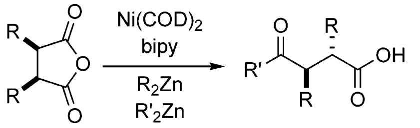
entry	R	R'	product ratio (R:R')	combined yield (%)
1	Ph	Et	19:1	91
2[a]	Ph	Et	19:1	87
3	Ph	Me	9:1	89
4	Me	Et	3:1	75
5	Ph	*i*Pr	>20:1	90
6	Me	*i*Pr	>20:1	90
7	Et	$TMSCH_2$	>20:1	78

[a] Reaction performed with 0.7 equiv of each diorganozinc reagent.

In qualitative experiments, we have observed that the alkylation of *cis*-1,2,3,6-tetrahydrophthalic anhydride **3** with Me_2Zn, catalyzed by Ni(COD)$_2$ and bipyridyl (bipy) (Table 1), is complete within 5 min; reaction with Et_2Zn requires 10 min, and reaction with Ph_2Zn requires approximately 20 min. Alkylation of **3** with a 1:1 mixture of Et_2Zn and Ph_2Zn provided a surprising result: Ph transfer was favored over Et transfer by a 19:1 margin. These results indicate that the mixed zinc reagent, PhZnEt, behaves differently than the independent reagents in the Ni-catalyzed cross-coupling. Although the relative rate of substituent transfer from Sn reagents containing a mixture of substituents is quite well-known (alkynyl > vinyl > aryl > alkyl),[18] we are unaware of any studies examining the relative propensity of akyl and aryl substituents from zinc in cross-coupling reactions.[19] For this reason, and to further investigate the potential transfer of both substituents from a parent diorganozinc reagent, we initiated a thorough evaluation of selective substituent transfer from diorganozinc reagents in Ni-catalyzed cross-couplings with anhydrides.

The alkylation of a cyclic anhydride with an organozinc reagent is efficiently catalyzed by Ni and a number of appropriate ligands. Catalyst precursors include both Ni(0) [Ni(COD)$_2$] and Ni(II) [Ni(acac)$_2$] sources, and compatible ligands include bipy, pyphos (**1**), 1,2-bis(diphenylphosphino)-ethane (dppe), and isopropylphosphinooxazoline (*i*PrPHOX) (**2**). Following the precedent of Knochel, these reactions have been shown to proceed more efficiently in the presence of a styrene promoter.[20]

Our survey of mixed zinc reagents began using Ni(COD)$_2$, bipy, and styrene to catalyze the alkylation of *cis*-1,2,3,6-tetrahydrophthalic anhydride **3**. Using a 1:1 ratio of Ph_2Zn and Et_2Zn, the alkylation of **3** proceeds in a 91% yield with 19:1 selectivity for transfer of the phenyl group. A sequence of reactions, performed with Ph_2Zn, Me_2Zn, Et_2Zn, *i*Pr$_2$Zn, and $(TMSCH_2)Zn$ to determine the relative propensity of substituent transfer from zinc, suggests that Ph is transferred most readily, followed by Me and Et (Figure 1). Much slower is the transfer of the hindered *i*Pr and CH_2TMS substituents. These observations suggest that aryl transfer is sufficiently faster than ethyl transfer to allow the use of commercially available Et_2Zn as the source of the nontransferable substituent.



(3)

Rate of transfer: Ph > Me > Et >> *i*Pr ~ CH_2TMS

Figure 1. Order of substituent transfer from mixed diorganozinc reagents.

As the range of commercially available diorganozinc nucleophiles is quite limited, we also examined the use of diorganozinc reagents formed in situ to generate mixed zinc reagents.[21] Nucleophiles prepared from corresponding aryl

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[12] (a) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Reddy, C. K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1496. (b) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895.

[13] von dem Bussche-Hünnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719.

[14] (a) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465. (b) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273.

[15] (a) Tan, L.; Chen, C.-y.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 711. (b) Forrat, V. J.; Prieto, O.; Ramón, D. J.; Yus, M. *Chem.—Eur. J.* **2006**, *12*, 4431.

[16] (a) Lipshutz, B. H.; Wood, M. R.; Tirado, R. *J. Am. Chem. Soc.* **1995**, *117*, 6126. (b) Jones, P.; Reddy, C. K.; Knochel, P. *Tetrahedron* **1998**, *54*, 1471. (c) Schinnerl, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett.* **2001**, *3*, 4259. (d) Soorukram, D.; Knochel, P. *Org. Lett.* **2004**, *6*, 2409.

[17] (a) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454. (b) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79. (c) Rimkus, A.; Sewald, N. *Org. Lett.* **2002**, *4*, 3289.

[18] Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

[19] Limited studies have been performed regarding the transfer of diorganozinc reagents to aldehydes: see refs 14−17.

[20] (a) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387. (b) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544.

[21] (a) Peña, D.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1836. (b) Kim, J. G.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4175.

bromides, *n*-butyllithium, and $ZnCl_2$ were used without purification (Table 2). The presence of residual salts (LiCl and LiBr) proved to have no noticeable effect on the selectivity of transfer from the mixed zinc reagent, providing the desired aryl keto acid in at least an 18:1 ratio over the ethyl adduct. Use of air-stable $Ni(acac)_2$ as the metal source also selectively provided the desired aryl adduct, providing a 15:1 ratio with a slightly decreased yield (entry 4). The electronic influence upon selectivity is illustrated by the selectivity of Ph transfer over 3,4,5-$(MeO)_3$Ph transfer in a 3:1 ratio (entry 6). It should be noted that for these experiments only 0.7 equiv of diorganozinc was utilized—in numerous examples, this represents transfer of the second substituent, a phenomenon which does not occur in the absence of a second diorganozinc reagent.

Table 2. Use of in Situ Nucleophiles in the Alkylation of **3** Catalyzed by $Ni(COD)_2$ and Bipy[a,b]

entry	R	R’	product ratio (R:R’)	combined yield (%)
1	Ph	Et	18:1	88
2	Ph	$TMSCH_2$	>20:1	83
3	*p*-OMePh	Et	19:1	76
4[c]	*p*-OMePh	Et	15:1	67
5	3,4,5-$(OMe)_3$Ph	Et	18:1	79
6	3,4,5-$(OMe)_3$Ph	Ph	1:3	82

[a] Reaction conditions: **3** (1 equiv), $Ni(COD)_2$ (5 mol %), bipy (6 mol %), styrene (10 mol %), and R_2Zn and R'_2Zn (0.7 equiv of each) in THF at 0−23 °C for 16 h. [b] R_2Zn formed in situ from ArBr, *n*BuLi, and $ZnCl_2$. [c] Reaction performed with $Ni(acac)_2$ (5 mol %).

The reaction also proceeds efficiently with more highly functionalized diorganozinc reagents. The alkylation of *cis*-1,2-cyclohexanedicarboxylic anhydride **4** was performed with a mixture of Et_2Zn and $(EtCO_2CH_2CH_2)_2Zn$ (eq 4) (Figure 2). Despite their relative similarities, the ester substituent transfers with a 5:1 selectivity over the Et substituent. As expected, use of $(TMSCH_2)_2Zn$ as the second zinc reagent results in nearly complete selectivity for transfer of the ester, providing the desired product in 71% yield.

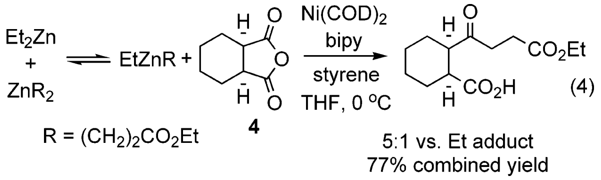


Figure 2. Addition of functionalized mixed zinc reagents.

After examination of the reaction under our standard conditions, we set out to determine whether high selectivity is also observed for other ligands known to facilitate this reaction in conjunction with $Ni(COD)_2$. Use of dppe as a ligand provides a relatively similar continuum of transfer propensity, with Ph transfer occurring more readily than Et or Me transfer (Table 3, entries 1−3). In this case, however, no selectivity was observed between Me and Et. Yields for these reactions are also generally lower than those observed for reactions with bipy.

Table 3. Alkylation of **3** Catalyzed by $Ni(COD)_2$ with Dppe or Pyphos[a]

entry	ligand	R	R’	product ratio (R:R’)	combined yield (%)
1	dppe	Ph	Et	10:1	64
2	dppe	Ph	Me	6:1	67
3	dppe	Et	Me	1:1	67
4	pyphos	Ph	Et	1:2	82
5	pyphos	Ph	Me	1:2	83
6	pyphos	Et	Me	2:1	86

[a] Reaction conditions: **3** (1 equiv), $Ni(COD)_2$ (5 mol %), ligand (6 mol %), styrene (10 mol %), 1.1 equiv of both R_2Zn and R'_2Zn, THF, 0−23 °C for 16 h.

Reactions run using pyphos as the ligand provide a distinct shift in the nature of transfer from the mixed zinc reagent (Table 3, entries 4−6). We observe relatively little substituent selectivity in any of the combinations tested. These results suggest that anhydride alkylation catalyzed by the Ni−pyphos system may proceed through a mechanism distinctly different from that observed for the Ni−bipy-catalyzed system or that some combination of ligand electronics and sterics significantly alters the transmetalation process. The relative selectivity of Et vs Me is also counterintuitive.

Table 4. Alkylation of **3** Catalyzed by $Ni(COD)_2$ and *i*PrPHOX[a]

entry	R	R’	products (R:R’)	combined yield (%)	ee (%) (R adduct)
1[b]	Ph			81	65
2[b]	Ph[c]			79	22
3	Ph	Et	10:1	78	75
4	Ph[c]	Et	10:1	73	63
5[d]	Ph[c]	Et	1.3:1	69	74
6	Ph[c]	$TMSCH_2$	>20:1	77	33
7[d]	Ph[c]	$TMSCH_2$	>20:1	72	44
8	Ph[c]	*i*Pr	>20:1	77	35
9[d]	Ph[c]	*i*Pr	>20:1	73	40

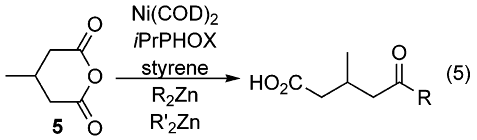
[a] Reaction conditions: **3** (1 equiv), $Ni(COD)_2$ (5 mol %), *i*PrPHOX (6 mol %), styrene (10 mol %), and R_2Zn and R'_2Zn (0.7 equiv of each) in THF, 0−23 °C for 16 h. [b] Used 1.4 equiv of R_2Zn. [c] R_2Zn prepared in situ from ArBr, *n*BuLi, and $ZnCl_2$ and used without further purification. [d] 5 equiv of R'_2Zn.

Knochel[12] and Bolm[14] have independently reported that the use of mixed zinc reagents affects enantioselectivities. Thus, in alkylation catalyzed by $Ni(COD)_2$ and *i*PrPHOX, we explored the effect of mixed zinc reagents on product enantioselectivity in conjunction with our study on the propensity of substituent transfer. Our results of this study are shown in Table 4. Although the selectivity of Ph transfer in the presence of Et_2Zn is less than that observed with the Ni−bipy-catalyzed system, the selectivity for Ph transfer is nearly complete when $i\mathrm{Pr}_2Zn$ or $(TMSCH_2)_2Zn$ is the second zinc reagent. Similar product selectivities are observed using commercially available Ph_2Zn or that prepared from bromobenzene and $ZnCl_2$.

It should be noted that the alkylative desymmetrization of cyclic anhydrides typically proceeds in lower enantioselectivity with the use of in situ prepared nucleophiles than with the salt-free commercially available species (entries 1 and 2). The use of mixed zinc species has significant effects upon alkylation product enantioselectivities. These effects, however, greatly depend on the relative amount and identity of the second zinc additive and are currently under further investigation.

Mixed zinc reagents were also utilized in the alkylative desymmetrization of 4-methylglutaric anhydride (**5**) catalyzed by $Ni(COD)_2$ and *i*PrPHOX (Table 5). As in the alkylation of the succinic anhydrides, a 1:1 ratio of Ph_2Zn and Et_2Zn primarily results in Ph transfer. Again, use of $i\mathrm{Pr}_2Zn$ or $(TMSCH_2)_2Zn$ with Ph_2Zn prepared in situ resulted in complete selectivity for Ph transfer. Unlike earlier results with the reaction of succinic anhydrides, the enantioselectivity of the alkylated glutaric anhydrides displays little dependence upon the nature of the second diorganozinc reagent.

Table 5. Alkylation of **5** Catalyzed by $Ni(COD)_2$ and *i*PrPHOX[a]

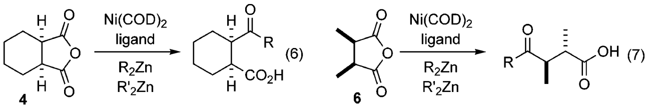


entry	R	R'	products (R:R')	combined yield (%)	ee (%) (R adduct)
1[b]	Ph	-		72	55
2[b]	Ph[c]	-		67	49
3	Ph	Et	12:1	79	54
4	Ph[c]	Et	17:1	63	54
5	Ph[c]	$TMSCH_2$	>20:1	74	58
6[b]	Et			78	62
7	Et	$TMSCH_2$	>20:1	74	58

[a] General conditions: **5** (1 equiv), $Ni(COD)_2$ (5 mol %), *i*PrPHOX (6 mol %), styrene (10 mol %), R_2Zn (0.7 equiv), R'_2Zn (0.7 equiv), in THF, 0−23 °C, 16 h. [b] Used 1.4 equiv of R_2Zn. [c] R_2Zn prepared in situ from ArBr, *n*BuLi, and $ZnCl_2$ and used without further purification.

Although initial screens were performed with anhydride **3**, other anhydrides, namely, 1,2-cyclohexanedicarboxylic anhydride (**4**) and 2,3-dimethylsuccinic anhydride (**6**), were also alkylated with mixed zinc reagents (Table 6) under Ni catalysis. These reactions proceed with selectivities similar to those observed with anhydride **3**. To further explore the potential of this method, entries 4−6 were performed with only 0.55 equiv of in situ formed bis(3,4,5-trimethoxyphenyl)zinc. This reaction, particularly under catalysis with bipy, demonstrates its utility, as both aryl groups are successfully transferred from approximately 50% of the diorganozinc reagent in producing the desired product in 76% yield.

Table 6. Alkylation of Other Anhydrides with Mixed Zinc Reagents[a,b]



AH	entry	ligand	R	R'	product ratio (R:R')	combined yield (%)
4	1	bipy	Ph	Et	>20:1	83
	2	dppe	Ph	Et	6:1	69
	3	pyphos	Ph	Et	1:2	73
6	4[c]	bipy	3,4,5-$(OMe)_3Ph$	Et	15:1	76
	5[c]	dppe	3,4,5-$(OMe)_3Ph$	Et	8:1	53
	6[c]	pyphos	3,4,5-$(OMe)_3Ph$	Et	2:1	68

[a] General reaction conditions: AH (1 equiv), $Ni(COD)_2$ (5 mol %), ligand (6 mol %), styrene (10 mol %), R_2Zn and R'_2Zn (0.7 equiv of each) in THF, 0−23 °C, 16 h. [b] Nucleophile prepared in situ from ArBr, *n*BuLi, and $ZnCl_2$. [c] Used 0.55 equiv of R_2Zn and R'_2Zn.

With these studies, we have demonstrated the utility of mixed zinc reagents as nucleophiles in the catalytic alkylation of carboxylic acid anhydrides and illustrated the relative transfer propensity of Ph, Et, Me, *i*Pr, and CH_2TMS in these alkylation reactions. The technique of using mixed zinc reagents with bipy, dppe, or *i*PrPHOX ligands obviates the use of an excess of a potentially expensive or difficult to prepare diorganozinc reagent.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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