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Use of $InCl_3$ as a Cocatalyst and a $Cl_2Pd(DPEphos)–P(2\text{-}Furyl)_3$ Catalyst System for One-Pot Hydrometalation–Cross-Coupling and Carbometalation–Cross-Coupling Tandem Processes

Mingxing Qian, Zhihong Huang, and Ei-ichi Negishi*

Herbert C. Brown Laboratories of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084

negishi@purdue.edu

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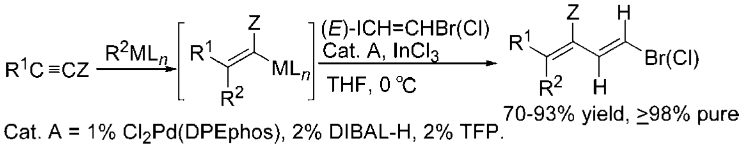
ABSTRACT



One-pot conversion of alkynes to regio- and stereodefined alkenylmetals containing Al and Zr via hydrometalation or carbometalation followed by their Pd-catalyzed cross-coupling with (*E*)-ICH═CHBr or (*E*)-ICH═CHCl proceeds cleanly and selectively to give the corresponding 1-halo-1,3-dienes in excellent yields using a catalyst system consisting of $Cl_2Pd(DPEphos)$, DIBAL-H, and TFP (catalyst A) with $InCl_3$ as a cocatalyst.

The one-pot synthesis of conjugated dienes via hydrometalation involving Al[1] and Zr[2] hydrides followed by Pd-catalyzed cross-coupling, as well as via Zr-catalyzed carboalumination and Pd-catalyzed cross-coupling,[3] was originally reported during between 1976 and 1978. In many cases, however, it was not only desirable but necessary to use either cocatalysts or stoichiometric promoters, and none have been superior to $ZnCl_2$ or $ZnBr_2$ as a cocatalyst for these processes.[3,4] Even so, these one-pot processes have still been inferior, in some highly demanding cases,[4f,5] to the process involving (i) hydrometalation or carbometalation, (ii) iodinolysis followed by isolation and purification of alkenyl iodides, (iii) lithiation with 2 equiv of *t*-BuLi in ether, (iv) transmetalation with dry $ZnCl_2$ or $ZnBr_2$ to generate preformed alkenylzinc derivatives, and (v) Pd-catalyzed cross-coupling.

In our recent attempts to improve the synthetic usefulness of the above-mentioned tandem processes for the syntheses of dienes and polyenes further, Pd-catalyzed cross-coupling reactions of (*E*)-ICH═CHBr[4d,f,g,6,7] and (*E*)-ICH═CHCl[7] have

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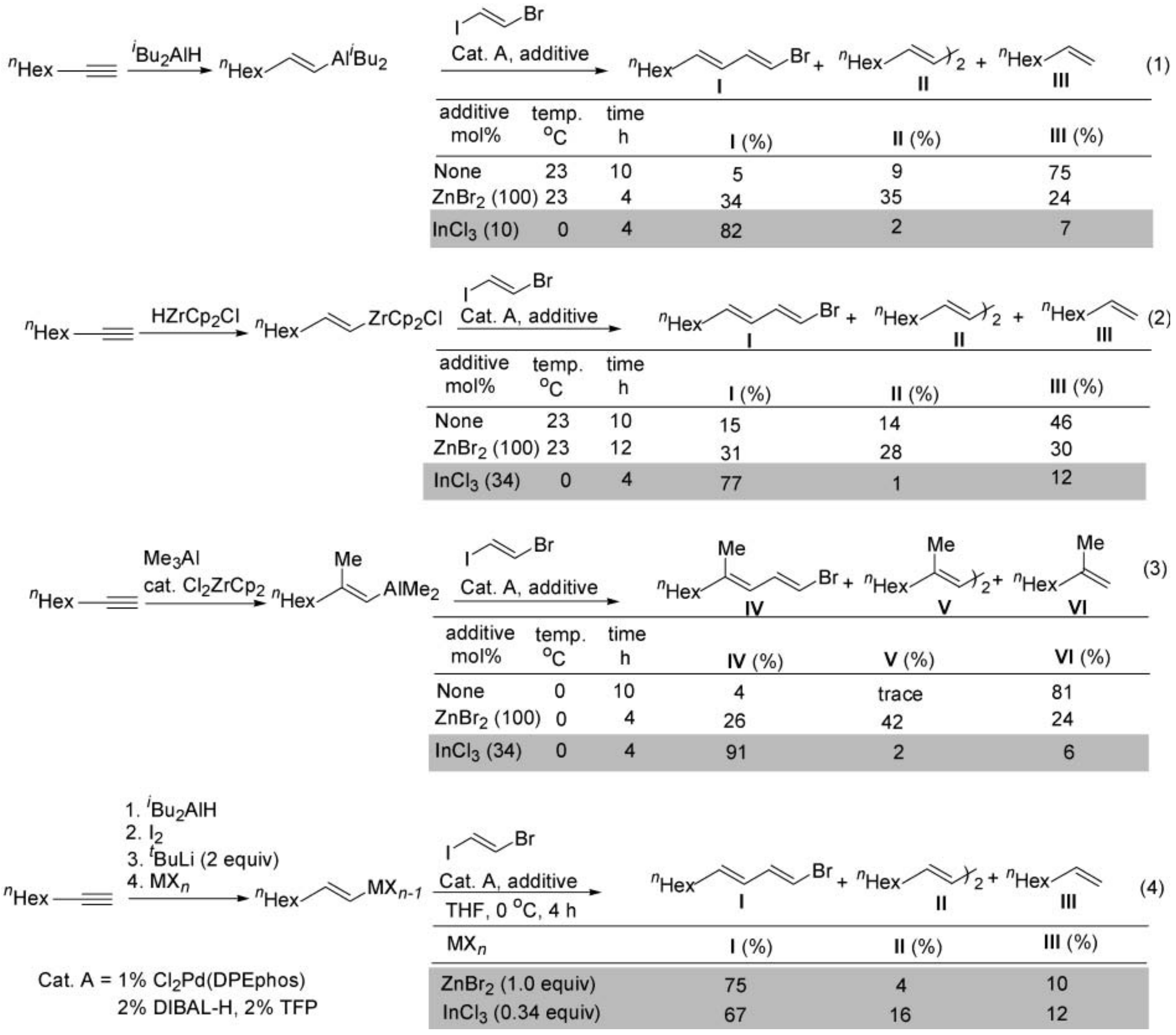
10.1021/ol049716f CCC: \$27.50

Scheme 1



(1)

additive mol%	temp. °C	time h	I (%)	II (%)	III (%)
None	23	10	5	9	75
$ZnBr_2$ (100)	23	4	34	35	24
$InCl_3$ (10)	0	4	82	2	7

(2)

additive mol%	temp. °C	time h	I (%)	II (%)	III (%)
None	23	10	15	14	46
$ZnBr_2$ (100)	23	12	31	28	30
$InCl_3$ (34)	0	4	77	1	12

(3)

additive mol%	temp. °C	time h	IV (%)	V (%)	VI (%)
None	0	10	4	trace	81
$ZnBr_2$ (100)	0	4	26	42	24
$InCl_3$ (34)	0	4	91	2	6

(4)

MX_n	I (%)	II (%)	III (%)
$ZnBr_2$ (1.0 equiv)	75	4	10
$InCl_3$ (0.34 equiv)	67	16	12

Cat. A = 1% Cl_2Pd(DPEphos)
2% DIBAL-H, 2% TFP

been investigated. While their Pd-catalyzed cross-coupling with alkynylzincs[4d,7] has been shown to be widely applicable and generally satisfactory, their Pd-catalyzed reactions with alkenyl,- aryl,- and alkylmetals containing Al, Zr, and others have proved to be much more demanding, and satisfactory results have, in the past, been obtained only in those cases where β,β-dialkyl-substituted alkenylalanes generated by Zr-catalyzed carboalumination were employed.[4f] Extensive screening and optimization of Pd catalysts and cocatalysts, as well as other parameters such as solvents, have therefore been conducted, and a system consisting of Cl_2Pd(DPEphos)[8] [typically 1 mol %, DPEphos = bis(2-diphenylphosphinophenyl)ether], tris(2-furyl)phosphine[9] (TFP) (typically 2 mol %), and $InCl_3$, but not $ZnCl_2$ or $ZnBr_2$, as a cocatalyst has proved to be uniquely satisfactory and distinctly superior to any of the previously developed protocols and all of the other procedures that have been examined in this study. Both the use of $InCl_3$[10] as a cocatalyst[11] and the demonstration of synthetically beneficial effects of double-phosphine catalyst systems appear to be unprecedented. Although $InBr_3$ was as effective as $InCl_3$, the latter was chosen, as it is less expensive, especially on a molar basis.

Representative experimental results are summarized in Scheme 1. For comparison, the results observed in the

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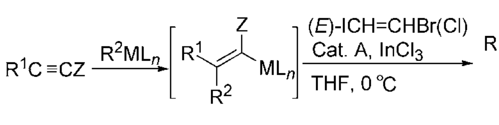
Table 1. Pd- and In-Cocatalyzed Hydrometalation−Cross-Coupling and Carbometalation−Cross-Coupling Tandem Processes for One-Pot Conversion of Alkynes into Stereo- and Regiodefined 1-Halo-1,3-dienes



Cat. A = 1% $Cl_2Pd(DPEphos)$, 2% DIBAL-H, 2% TFP

entry	$R^1C{\equiv}CZ$	R^2ML_n	ICH=CHX	mol % $InCl_3$	time, h	yield,[a] %		
						product	dimer	monomer
1	${}^nHexC{\equiv}CH$	HAl^iBu_2	ICH=CHBr	34	4	85 (81[b])	<1	5
2	${}^nHexC{\equiv}CH$	HAl^iBu_2	ICH=CHBr	10	8	82	2	7
3	${}^nHexC{\equiv}CH$	HAl^iBu_2	ICH=CHBr	7	10	76	4	15
4	${}^nHexC{\equiv}CH$	HAl^iBu_2	ICH=CHCl	34	4	87 (85[b])	<1	4
5	${}^nHexC{\equiv}CH$	HAl^iBu_2	ICH=CHCl	10	8	80	<1	11
6	${}^nHexC{\equiv}CH$	$HZrCp_2Cl$	ICH=CHBr	34	4	77	1	12
7	${}^nHexC{\equiv}CH$	$HZrCp_2Cl$	ICH=CHBr	10	8	76	3	13
8	${}^nHexC{\equiv}CH$	$HZrCp_2Cl$	ICH=CHBr	7	10	70	6	19
9	$PhC{\equiv}CH$	$HZrCp_2Cl$	ICH=CHBr	34	4	89 (84[b])	<1	5
10	$EtC{\equiv}CEt$	$HZrCp_2Cl$	ICH=CHBr	34	4	86 (82[b])	<1	c
11	${}^nHexC{\equiv}CH$	$Me_3Al{-}Cl_2ZrCp_2$	ICH=CHBr	34	4	91 (87[b])	2	6
12	${}^nHexC{\equiv}CH$	$Me_3Al{-}Cl_2ZrCp_2$	ICH=CHBr	10	8	85	3	10
13	${}^nHexC{\equiv}CH$	$Me_3Al{-}Cl_2ZrCp_2$	ICH=CHBr	7	10	77	8	12
14	${}^nHexC{\equiv}CH$	$Me_3Al{-}Cl_2ZrCp_2$	ICH=CHCl	34	4	95 (93[b])	<1	<1
15	$HOCH_2CH_2C{\equiv}CH$	$Me_3Al{-}Cl_2ZrCp_2$	ICH=CHBr	34	10	80 (70[b])	<1	c

[a] Yield by GLC. [b] Isolated yield. [c] Not readily detected by GLC.

corresponding reactions of preformed (*E*)-1-octenylzinc bromide and tris[(*E*)-1-octenyl]indium are also shown in eq 4 in Scheme 1. These results indicate the following: (1) In none of the tandem reactions shown in eqs 1−3 were the previously developed Pd−Zn double-metal-catalyzed procedures satisfactory, even in cases where the optimized catalyst system (catalyst A) consisting of 1 mol % $Cl_2Pd(DPEphos)$, 2 mol % TFP, and 2 mol % DIBAL-H for reduction of $Cl_2Pd(DPEphos)$ (vide infra) was used. (2) In contrast, the Pd−In double-metal-catalyzed process employing catalyst A has been highly and uniquely satisfactory. (3) And yet, In is not superior to Zn in the corresponding stoichiometric reactions of alkenylmetals containing Zn and In. Furthermore, the Pd−In cocatalysis is superior to either of the reactions represented by eq 4 in Scheme 1, pointing to favorable synergistic effects associated with Al−In and Zr−In combinations. Irrespective of the precise mechanistic interpretation, the Pd−In double-metal-catalyzed protocol presented in eqs 1−3 of Scheme 1 has provided a one-pot tandem procedure that is far superior to any previously developed ones for the indicated transformations.

As indicated earlier, one of our recent papers[4f] described a satisfactory one-pot conversion of terminal alkynes into (*E,E*)-1-bromo-4-methyl-1,3-dienes via (i) carboalumination with $Me_3Al{-}Cl_2ZrCp_2$ and (ii) cross-coupling in the presence of 5 mol % $Pd(PPh_3)_4$, 1 equiv of $ZnBr_2$, and DMF used as a cosolvent for the synthesis of unsymmetrical carotenoids. The use of THF as a solvent led to very low product yields. It was also necessary to evaporate CH_2Cl_2 used for Zr-catalyzed methylalumination before the addition of DMF and/or THF. More critically, even this procedure was found to be rather unsatisfactory in cases where β-monosubstituted alkenylmetals containing Al or Zr were used. The procedure reported herein has solved all of the problems mentioned above and appears to be widely applicable and generally dependable, as indicated by the results summarized in Table 1. All of the isolated products were of ≥98% isomeric purity by ^1H and ^{13}C NMR spectroscopy and GLC analysis.

It may be worth describing in some detail how uniquely advantageous catalyst A consisting of $Cl_2Pd(DPEPhos)$ and TFP is, even though no persuasive rationalization can be presented at this time. In view of multistage nature of Pd-catalyzed cross-coupling, it was envisioned that optimal Pd catalysts for two or more microsteps may be different from one another. On this basis, various two-phosphine catalyst systems were screened initially for the reaction of preformed (*E*)-1-octenylzinc bromide with (*E*)-ICH=CHBr (1.2 equiv) at 23 °C in THF, and the combination of $Cl_2Pd(DPEphos)$ and TFP, i.e., catalyst A, has been found to be distinctly superior to any others. Specifically, the use of one-phosphine Pd catalyst systems (5 mol % in Pd) such as $Pd(PPh_3)_4$ (18%), $Pd(t\text{-}Bu_3P)_2$ (12%), $Pd_2(dba)_3{-}2TFP$ (24%), $Cl_2Pd(dppf){-}2DIBAL\text{-}H$ (40%), and $Cl_2Pd(DPEphos){-}2DIBAL\text{-}H$ (43%) all led to the disappointingly low yields indicated in parentheses. Various binary combinations of the

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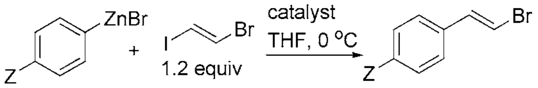
(11) For the use of $InBr_3$ as a cocatalyst in the Pd-catalyzed cross-coupling of terminal alkynes with aryl iodides, see: Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527. We thank Prof. N. Sakai for sharing their results with us before publication.

above-mentioned phosphines were then screened, and catalyst A was found to be by far the most satisfactory combination, as shown in eq 4 in Scheme 1. On the other hand, all of the others, including $Cl_2Pd(DPEphos)-dppf$ (31%), $Cl_2Pd(DPEphos)-2PPh_3$ (39%), $Cl_2Pd(dppf)-2TFP$ (51%), $Cl_2Pd(dppf)-2PPh_3$ (44%), $Cl_2Pd(dppf)-DPEphos$ (38%), $Cl_2Pd(PPh_3)_2-dppf$ (42%), $Pd(t\text{-}Bu_3P)_2-dppf$ (38%), $Pd(t\text{-}Bu_3P)_2-2TFP$ (32%), $Pd(t\text{-}Bu_3P)_2-DPEphos$ (17%), and $Pd(t\text{-}Bu_3P)_2-2PPh_3$ (21%), led to low product yields accompanied by extensive formation of byproducts. In cases where Pd(II) complexes were used, DIBAL-H was used as an external reducing agent. Mysteriously, even $Cl_2Pd(TFP)_2-DPEphos$ (36%) and $Pd_2(dba)_3-2DPEphos-4TFP$ (37%) were distinctly and unmistakably inferior to catalyst A. At present, the unique superiority of catalyst A over all of the others tested remains as a mechanistic puzzle to be clarified.

The superior catalytic activity of catalyst A extends beyond the 1-halo-1,3-diene synthesis described above. Thus, it has substantially improved the reaction of preformed arylzinc derivatives with (*E*)-ICH═CHBr, as indicated in Scheme 2.

Scheme 2



Z	catalyst	yield,[a] %
H	$Cl_2Pd(DPEphos)$-TFP-DIBAL-H	94 (90[b])
NC	$Cl_2Pd(DPEphos)$-TFP-DIBAL-H	76 (70[b])
MeO	$Cl_2Pd(DPEphos)$-TFP-DIBAL-H	85 (82[b])
MeO	$Cl_2Pd(DPEphos)$	14
MeO	$Pd_2(dba)_3$-TFP	7
MeO	$Pd_2(dba)_3$-dppf	10
MeO	$Cl_2Pd(DPEphos)$-TFP-DIBAL-H	15[c]

[a] Yield by GLC. [b]Isolated yield. [c]$(p\text{-}MeOC_6H_4)_3In$ used in place of $p\text{-}MeOC_6H_4ZnBr$.

It has become increasingly clear from this and other recent works reported by us and others that selective Pd- or Ni-catalyzed cross-coupling reactions involving 1,1-[12] and 1,2-dihaloalkenes[7c] tend to be considerably more capricious and demanding but that satisfactory procedures may nevertheless be developed through optimization of (i) catalysts, especially ligands, (ii) cocatalysts, and (iii) solvents. In this paper, the use of $InCl_3$ as a cocatalyst and/or a double-phosphine catalyst system consisting of $Cl_2Pd(DPEphos)$ and TFP has been shown to be effective in selective monosubstitution of 1,2-dihaloethylenes.

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

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