Pd-catalyzed cross-coupling reactions exhibiting catalyst turnover numbers (TONs) exceeding one million

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This paper is dedicated to Professor Keith Smith in recognition and appreciation of his pioneering contribution to the development of green organic synthesis

Abstract

Pd-catalyzed cross-coupling giving aryl–aryl, alkenyl–aryl, aryl–alkenyl, alkynyl–aryl, and alkynyl–alkenyl products exhibited ultra-high turnover numbers (TONs) of $0.7{\times}10^7$~$0.69{\times}10^9$ by using organozincs generated *in situ* by treatment of the corresponding organolithiums with dry $ZnBr_2$. Additionally, the hydrozirconation–Pd-catalyzed cross-coupling tandem processes via treatment of 1-alkynes with $^iBu_2AlH$-$ZrCp_2Cl_2$ followed by selective (≥98%) alkenyl–alkenyl coupling with either (*E*)- or (*Z*)-ethyl 3-bromoacrylate exhibited high TONs of $0.9{\times}10^5$~$0.81{\times}10^7$. Furthermore, Pd-catalyzed cross-coupling of 2-thienylzinc bromide and 1-iodo-4-nitrobenzene also showed a high TON of $0.87{\times}10^5$.

Keywords: Pd-catalyzed cross-coupling, Negishi coupling, cross-coupling involving aryl, alkenyl, alkynyl, and heteroaryl groups, Pd-catalyst turnover numbers, Pd(DPEphos)Cl$_2$, PEPPSI-IPr, PEPPSI-IPent

Introduction

In any catalytic reaction, catalysts must be regenerated in their original forms. In reality, however, catalysts do become gradually decomposed and hence inactivated, resulting in finite turnover numbers (TONs hereafter). For "green" organic syntheses involving catalytic processes, catalyst TON is a critically important factor affecting the economical aspects of such processes. Several years ago, we found[1] that various representative classes of Pd-catalyzed cross-coupling of the Negishi version using Zn as the metal countercation in the organometallic reagent, would display TONs up to around 10^6. Even if a catalyst costs a million dollars (\$$10^6$) per mol the

effective cost of the catalyst per production of one mol of a desired organic product is a mere \$1/mol. On this basis, we opted to not pursue this matter beyond the TON level of 10^6. Incidentally, the use of some other metal countercations under allegedly optimal conditions led to TONs up to 10^5 (observed with Al, B, In, or Zr) or in the range of 10^3~10^4 (observed with Mg, Mn, or Sn).

More recently, we have been informed that, in view of potential toxicity concerns, it is desirable to further improve TONs of Pd-catalyzed cross-couplings beyond the 10^6 level. On this basis and on the basis of our own scientific curiosity, we decided to pursue the TONs of representative Pd-catalyzed cross-coupling reactions beyond the previously observed range of up to around 10^6, focusing our attention on Zn and a few other superior metals, such as Al, B, and Zr as the metal counteractions.

Results and Discussion

In order to observe high TONs in a reliable manner, we paid careful attention to avoiding false results due to contamination of the reaction system or vessel with residual catalyst, and erratic results due to any other factors. The results of the determination of TONs of the cross-coupling reactions involving aryl-, alkenyl-, or alkynylzinc bromides with aryl- or alkenyl- iodides in the presence of catalytic amounts of Pd(DPEphos)Cl$_2$ are summarized in Table 1. For each Entry, a series of runs were followed by a blank run executed without addition of the catalyst under otherwise the same conditions. In each case, no formation of the desired product was observed. Furthermore, the catalyst solutions were prepared by a series of ten-fold dilutions with dry THF for high internal consistency among a series of experiments.

A series of reactions were initially performed at 23 °C. After observing product yields of <65% over 24 h, such reaction mixtures were heated to 70 °C, and they were further examined, confirming product yields of <65% even after 24 h at 70 °C. The TON for each case, i.e., each Entry, was calculated based on the last run exhibiting ≥65% yield of the desired product. All five classes of Pd-catalyzed cross-couplings shown in Table 1 exhibited unprecedentedly high TONs of the order of $10^7 \sim 10^9$. Many of the yield and TON figures represent averages of two or more runs. Moreover, each cross-coupling reaction was run at least at four catalyst concentration levels ($1 \sim 10^{-7}$ mol%), and a blank run without addition of the catalyst was also examined under otherwise the same conditions to avoid false results due to contamination.

The bidentate phosphine ligand DPEphos, bis[(2-diphenylphosphino)phenyl] ether,[2] is superior to some of the widely used monodentate phosphines, such as PPh$_3$, and TFP [tris(2-furyl)phosphine],[3] and the bidentate phosphine ligands, including dppf [1,1′-bis(diphenylphosphino)ferrocene][4], at low catalyst loading levels. The Pd(DPEphos)Cl$_2$-catalyzed cross-coupling reaction of PhZnBr(LiBr) with p-Tol-I exhibited an unprecedentedly high TON of 0.69×10^9. Although not listed in Table 1, the previously observed[1] TON of the reaction of PhZnBr(LiBr) with p-Tol-I catalyzed by Pd(dppf)Cl$_2$ was 0.35×10^7. The use of
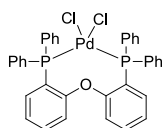
$Ni(PPh_3)_2Cl_2$ in this reaction was also briefly investigated.[5] The desired biaryl was obtained in 98% yield with 1 mol% of $Ni(PPh_3)_2Cl_2$. However, the yield decreased to 49% (24 h at 70 °C) at the 0.1 mol% level.

Table 1. Reaction of aryl-, alkenyl-, and alkynylzinc derivatives with aryl and alkenyl iodides in the presence of $Pd(DPEphos)Cl_2$

$$R^1ZnL_m \quad + \quad R^2I \xrightarrow[\text{THF}]{\text{cat. } Pd(DPEphos)Cl_2{}^c} R^1{-}R^2$$

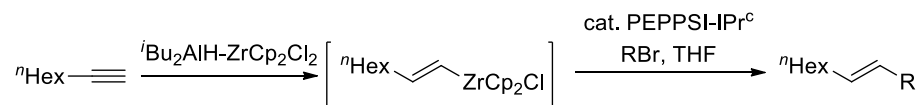| Entry	$R^1ZnL_m{}^a$	R^2I	$Pd(DPEphos)Cl_2$ (mol %)	T (°C)	Time (h)	$R^1{-}R^2$ (%)	R^2I (%)	TON[b]
1	PhZnBr(LiBr)	p-Tol-I	1	23	12	99	<1	
	PhZnBr(LiBr)	p-Tol-I	10^{-1}	23	24	97	<1	
	PhZnBr(LiBr)	p-Tol-I	10^{-4}	70	24	91	4	
	PhZnBr(LiBr)	p-Tol-I	10^{-6}	70	24	82	10	
	PhZnBr(LiBr)	p-Tol-I	10^{-7}	70	24	69	20	0.69×10^9
2	(E)-^{n}OctCH=CHZnBr(LiBr)	PhI	1	23	12	98	<1	
	(E)-^{n}OctCH=CHZnBr(LiBr)	PhI	10^{-2}	70	24	96	<1	
	(E)-^{n}OctCH=CHZnBr(LiBr)	PhI	10^{-6}	70	24	78	8	0.78×10^8
	(E)-^{n}OctCH=CHZnBr(LiBr)	PhI	10^{-7}	70	24	35	42	
3	PhZnBr(LiBr)	(E)-^{n}BuCH=CHI	1	23	15	98	<1	
	PhZnBr(LiBr)	(E)-^{n}BuCH=CHI	10^{-3}	70	15	95	<1	
	PhZnBr(LiBr)	(E)-^{n}BuCH=CHII	10^{-5}	70	24	80	6	
	PhZnBr(LiBr)	(E)-^{n}BuCH=CHI	10^{-6}	70	24	70	13	0.70×10^8
	PhZnBr(LiBr)	(E)-^{n}BuCH=CHI	10^{-7}	70	24	12	65	
4	^{n}PrC≡CZnBr(LiBr)	PhI	1	23	15	98	<1	
	^{n}PrC≡CZnBr(LiBr)	PhI	10^{-4}	70	24	86	4	
	^{n}PrC≡CZnBr(LiBr)	PhI	10^{-5}	70	24	72	12	0.72×10^7
	^{n}PrC≡CZnBr(LiBr)	PhI	10^{-6}	70	24	28	50	
5	PhC≡CZnBr(LiBr)	(E)-^{n}OctCH=CHI	1	23	15	98	<1	
	PhC≡CZnBr(LiBr)	(E)-^{n}OctCH=CHI	10^{-3}	70	24	95	<1	
	PhC≡CZnBr(LiBr)	(E)-^{n}OctCH=CHI	10^{-5}	70	24	70	20	0.70×10^7
	PhC≡CZnBr(LiBr)	(E)-^{n}OctCH=CHI	10^{-6}	70	24	35	53	

[a] $R^1ZnBr(LiBr)$ indicates that it was generated in situ by treating R^1Li with dry $ZnBr_2$. [b] TON was caculated for the case where the yield of $R^1{-}R^2$ exceeds 65% with the lowest amount of $Pd(DPEphos)Cl_2$. [c] $Pd(DPEphos)Cl_2$:

The alkenyl–aryl coupling of (E)-^{n}OctCH=CHZnBr(LiBr) with PhI and the aryl–alkenyl coupling of PhZnBr(LiBr) with (E)-^{n}BuCH=CHI exhibited TONs of 0.78×10^8 and 0.70×10^8, respectively. TONs of 0.72×10^7 and 0.70×10^7 were observed in the cases of the alkynyl–aryl coupling of ^{n}PrC≡CZnBr(LiBr) with PhI and the alkynyl–alkenyl coupling of PhC≡CZnBr(LiBr) with (E)-^{n}OctCH=CHI, respectively.
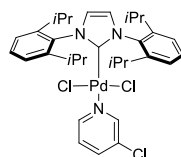
Recently, we developed a highly selective synthesis of conjugated dienoic and trienoic esters *via* alkyne elementometalation–Pd-catalyzed cross-coupling tandem processes.[6] (E)-Alkenyl-zirconium derivatives generated *in situ* by treating 1-alkynes with ^{i}Bu$_2$AlH-ZrCp$_2$Cl$_2$[7] undergo highly stereoselective alkenyl-alkenyl coupling with either ethyl (E)[8]- or (Z)[9]-3-bromoacrylate in the presence of 1 mol% of PEPPSI-IPr (pyridine-enhanced precatalyst preparation stabilization and initiation)[10] to provide various conjugated dienoic and trienoic esters in ≥98% stereoselectivity. High TONs of $0.60 \sim 0.65 \times 10^5$ in hydrometalation–Pd(dppf)Cl$_2$-catalyzed cross-coupling tandem reactions involving B, Al, and Zr (ZnBr$_2$ was added after hydrometalation) were observed.[1]

For economic and other reasons, it is desirable to use the bromides as coupling partners. In general, however, the Pd-catalyzed cross-coupling reactions of organic bromides have been found to be more sluggish and, hence, less favorable than the corresponding reactions of iodides. To determine the efficiency of hydrozirconation–Pd-catalyzed cross-coupling tandem processes recently developed in our laboratories,[6] we examined TONs of the cross-coupling reactions between (E)-^{n}HexCH=CHZrCp$_2$Cl with ethyl (E)- or (Z)-3-bromoacrylate, and the results are summarized in Table 2. Both reactions provided the desired conjugated dienoic esters (≥98% stereoselectivity) with high TONs of 0.81×10^7 and 0.90×10^5, respectively.

Table 2. High turnover numbers observed in hydrozirconation–Pd-catalyzed cross-coupling tandem reactions producing conjugated dienes

$$^{n}Hex \longrightarrow\!\!\!\equiv \xrightarrow{^{i}Bu_2AlH\text{-}ZrCp_2Cl_2} \left[^{n}Hex \diagdown\!\!\diagup ZrCp_2Cl \right] \xrightarrow[RBr,\ THF]{cat.\ PEPPSI\text{-}IPr^{c}} {}^{n}Hex \diagdown\!\!\diagup R$$

Entry	RBr	PEPPSI-IPr (mol %)	T (ºC)	Time (h)	Product (%)	RBr (%)	TON[a]
1	(Z)-BrCH=CHCO$_2$Et	1	23	15	98	<1	
	(Z)-BrCH=CHCO$_2$Et	10^{-1}	23	15	95	2	
	(Z)-BrCH=CHCO$_2$Et	10^{-3}	23	15	50	50	
			70[b]	24	90	5	0.90×10^5
	(Z)-BrCH=CHCO$_2$Et	10^{-4}	23	15	10	85	
			70[b]	24	40	50	
2	(E)-BrCH=CHCO$_2$Et	1	23	15	98	<1	
	(E)-BrCH=CHCO$_2$Et	10^{-1}	23	15	97	<1	
	(E)-BrCH=CHCO$_2$Et	10^{-3}	23	24	88	6	
	(E)-BrCH=CHCO$_2$Et	10^{-5}	70	24	81	12	0.81×10^7
	(E)-BrCH=CHCO$_2$Et	10^{-6}	70	24	28	62	

[a] TON was caculated for the case where the yield of coupled product exceeds 65% with the lowest amount of PEPPSI-IPr. [b] The reaction was initially run at 23 ºC for 15 h, then was refluxed. [c] PEPPSI-IPr:

Table 3. High turnover numbers observed in Pd-catalyzed cross-coupling of arylzinc and heteroarylzinc reagents with aryl iodides

$$R^1ZnL_m \quad + \quad R^2I \quad \xrightarrow{\text{cat. PdL}_n,\ \text{THF}} \quad R^1{-}R^2$$

Entry	R^1ZnL_m [a]	R^2I	PdL_n (mol %)	T (°C)	Time (h)	$R^1{-}R^2$ (%)	R^2I (%)	$R^1{-}R^1$ (%)	TON[b]
1[c]	PhZnBr(LiBr)	4-iodobenzonitrile	1	23	15	93	<1	5	
	PhZnBr(LiBr)	4-iodobenzonitrile	10^{-3}	70	24	88	<1	10	
	PhZnBr(LiBr)	4-iodobenzonitrile	10^{-4}	70	24	83	<1	13	0.83×10^6
	PhZnBr(LiBr)	4-iodobenzonitrile	10^{-5}	70	24	30	50	15	
2[d]	2-thienylzinc bromide	1-iodo-4-nitrobenzene	10^{-1}	23	24	97	<1	2	
	2-thienylzinc bromide	1-iodo-4-nitrobenzene	10^{-2}	70	24	95	<1	3	
	2-thienylzinc bromide	1-iodo-4-nitrobenzene	10^{-3}	70	24	87	5	3	0.87×10^5
	2-thienylzinc bromide	1-iodo-4-nitrobenzene	10^{-4}	70	24	10	83	4	
	2-thienylzinc bromide	1-iodo-4-nitrobenzene	10^{-3} [c]	70	24	32	60	5	

[a] $R^1ZnBr(LiBr)$ indicates that it was generated in situ by treating R^1Li with dry $ZnBr_2$. [b] TON was caculated for the case where the yield of $R^1{-}R^2$ exceeds 65% with the lowest amount of catalyst. [c] Pd(DPEphos)Cl$_2$ was used. [d] PEPPSI-IPent was used.
PEPPSI-IPent:
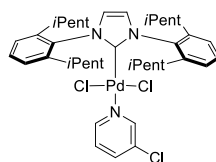
In order to illustrate the high tolerance of functional groups, we also examined the TON of the cross-coupling reaction of PhZnBr(LiBr) with 4-iodobenzonitrile (Table 3, entry 1) in the presence of Pd(DPEphos)Cl$_2$. A high TON of 0.83×10^6 was also observed in this reaction to provide the coupled product [1,1'-biphenyl]-4-carbonitrile. However, some quantities of a homocoupled biphenyl side product were observed in the reactions.

Heterobiaryls have attracted significant attention from the scientific community due to their wide range of pharmacological activities. The Pd-catalyzed cross-coupling reaction provides a very efficient method for the preparation of such compounds. However, this procedure generally suffers from high catalyst loading due to palladium catalyst poisoning by sulfur- and nitrogen-containing compounds. Negishi cross-coupling reactions using organozincs of generally higher reactivity relative to other organometallic reagents are attractive alternatives for achieving high TONs for the synthesis of heteroaryl compounds, since they typically require milder reaction conditions and shorter reaction times. PEPPSI-IPent has been proven to be an excellent catalyst for these demanding cross-coupling reactions to produce an array of biaryl and heterobiaryl

compounds bearing various functional groups in excellent yields under mild reaction conditions.[11] In view of the importance of heterobiaryl compounds, we also examined the TON of the cross-coupling reaction of 2-thienylzinc bromide and 1-iodo-4-nitrobenzene in the presence of PEPPSI-IPent. As shown in entry 2 of Table 3, a high TON of 0.87×10^5 was obtained for the preparation of 2-(4-nitrophenyl)thiophene. In order to demonstrate the high efficiency of PEPPSI-IPent, the cross-coupling reaction of 2-thienylzinc bromide and 1-iodo-4-nitrobenzene was also performed using Pd(DPEphos)Cl_2 as catalyst under similar reaction conditions. With 10^{-3} mol% of Pd(DPEphos)Cl_2, 2-(4-nitrophenyl)thiophene was formed in 32% yield. While 2-(4-nitrophenyl)thiophene was formed in 87% yield using 10^{-3} mol% of PEPPSI-IPent. Some other solvents, such as DMF, THF/DMF (2:1), THF/NMP (2:1), and 1,4-dioxane, were also surveyed in this reaction, but there was little influence on the TON of this reaction.

Conclusions

1. Unprecedentedly high turnover numbers (TONs) of the order of $10^7 \sim 10^9$ have been observed for aryl–aryl (up to 10^9), alkenyl–aryl, i.e., $R^1R^2C=CHM + ArI$, or aryl–alkenyl, i.e., $ArM + ICH=CR^1R^2$ $(0.70 \sim 0.78 \times 10^8)$, alkynyl–aryl, i.e., $RC≡CM + ArI$, and alkynyl–alkenyl, i.e., $RC≡CM + ICH=CR^1R^2$ $(0.70 \sim 0.72 \times 10^7)$ cases of the Pd-catalyzed cross-coupling using organometals generated *in situ* by treatment of the corresponding organolithiums with dry ZnBr$_2$. Although tentative, the observed order of aryl > alkenyl > alkynyl with respect to the observed TONs might be associated with the relative stabilities of the aryl, alkenyl, and alkynyl groups under the reaction conditions.

2. (*E*)-Alkenylzirconium derivatives generated *in situ* by treating 1-alkynes with ^{i}Bu$_2$AlH-ZrCp$_2$Cl$_2$[7] undergo stereospecific (≥98%) alkenyl–alkenyl coupling with either ethyl (*E*)- or (*Z*)-3-bromoacrylate to exhibit the high TONs of 0.81×10^7 and 0.90×10^5, respectively.

3. PEPPSI-IPent-catalyzed cross-coupling of 2-thienylzinc bromide and 1-iodo-4-nitrobenzene to produce heterobiaryl 2-(4-nitrophenyl)thiophene exhibits a high TON of 0.87×10^5.

4. Although not discussed in detail here, preliminary observations indicate that Pd-catalyzed cross-coupling with 1-halo-1-alkynes may not readily lead to the production of 1,2-disubstituted alkynes in high yields and high TONs.

Experimental Section

General. All glassware was flame-dried under vacuum, and the reactions were conducted under argon. THF and diethyl ether were dried and distilled from sodium/benzophenone under argon. $ZnBr_2$ was flame-dried *in vacuo*. Pd(DPEPhos)Cl$_2$ was prepared by the standard method.[12] PEPPSI-IPr, PEPPSI-IPent and 2-thienylzinc bromide solution were purchased from Aldrich and used as received. ^1H and ^{13}C NMR spectra were recorded in CDCl$_3$ on a Varian Inova-300 spectrometer. Chemical shifts are reported in parts per million (ppm) using CHCl$_3$ as the reference peak. The reactions were monitored by gas chromatography (GC) using an HP 7890A GC and an HP-5 (30 m × 0.32mm, 0.25μm) capillary column, with appropriate hydrocarbons as internal standards. Thin-layer chromatography (TLC) was carried out on Merck Glass Silica Gel 60 F-254 plates. Flash chromatographic separations were performed with 230 – 400 mesh silica gel 60 and hexanes.

Pd-catalyzed cross-coupling of aryl-, alkenyl-, or alkynylzincs with aryl or alkenyl iodides. Representative procedure A. 4-Methylbiphenyl.[13] To a solution of iodobenzene (265 mg, 1.3 mmol) in THF (2 mL) cooled to –78 °C was added dropwise *"*BuLi (0.52 mL, 2.5 M in hexanes, 1.3 mmol). The resultant solution was stirred at –78 °C for 30 min, followed by addition of a solution of dry $ZnBr_2$ (332 mg, 1.3 mmol) in THF (1 mL). The mixture was stirred at –78 °C for 10 min, and warmed to 0 °C over 20 min. 4-Iodotoluene (218 mg, 1 mmol) and Pd(DPEPhos)Cl$_2$ (100 μL, 10^{-5} M, 10^{-6} mmol in THF) were added, and the resultant mixture was heated at reflux. After 24 h, GC analysis indicated the title compound was formed in 82% yield. The reaction mixture was quenched with water, extracted with ether, dried over anhydrous MgSO$_4$, filtered, and concentrated. Flash chromatography (silica gel, hexane) afforded 134 mg (80%) of the title compound. ^1H NMR (300 MHz, CDCl$_3$) δ 2.36 (s, 3 H), 7.21 (d, *J* 7.9 Hz, 2 H), 7.28 (t, *J* 7.3 Hz, 1 H), 7.39 (t, *J* 7.3 Hz, 2 H), 7.47 (d, *J* 7.9 Hz, 2 H), 7.55 (d, *J* 7.8 Hz, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.0, 126.9 (3C), 126.9 (2C), 128.7 (2C), 129.4 (2C), 136.9, 138.3, 141.1.

(*E*)-Dec-1-enylbenzene.[14] The title compound was prepared according to **Representative procedure A except** that (*E*)-1-iododecene and iodobenzene were used instead of iodobenzene and 4-iodotoluene. The reaction mixture was heated at reflux for 24 h, and the title compound was obtained in 78% GLC yield. ^1H NMR (300 MHz, CDCl$_3$) δ 0.88 (t, *J* 6.8 Hz, 3 H), 1.27-1.48 (m, 12 H), 2.17-2.23 (m, 2 H), 6.19-6.26 (m, 1 H), 6.38 (d, *J* 15.6 Hz, 1 H), 7.15-7.40 (m, 5 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.1, 22.7, 29.3 (2C), 29.4, 29.5, 31.9, 33.0, 125.8 (2C), 126.6, 128.4 (2C), 129.7, 131.1, 137.9.

(*E*)-Hex-1-enylbenzene.[14] The title compound was prepared according to **Representative procedure A** except that (*E*)-1-iodohexene was used instead of 4-iodotoluene. The reaction mixture was heated at reflux for 24 h, and the title compound was obtained in 70% GLC yield. ^1H NMR (300 MHz, CDCl$_3$) δ 0.96 (m, 3 H), 1.34-1.54 (m, 4 H), 2.24 (q, *J* 6.6 Hz, 2 H), 6.20-6.30 (m, 1 H), 6.40 (d, *J* 15.6 Hz, 1 H), 7.17-7.23 (m, 1 H), 7.28-7.38 (m, 4 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.9, 22.2, 31.5, 32.7, 125.8 (2C), 126.7, 128.4 (2C), 129.7, 131.1, 137.9.

Pent-1-ynylbenzene.[15] The title compound was prepared according to **Representative procedure A** except that 1-pentyne and iodobenzene were used instead of iodobenzene and 4-iodotoluene in the amount of Pd(DPEPhos)Cl$_2$ (100 μL, 10^{-4} M, 10^{-5} mmol). The reaction mixture was heated at reflux for 24 h, and the title compound was obtained in 72% GLC yield. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.06 (t, *J* 7.2 Hz, 3 H), 1.58-1.70 (m, 2 H), 2.40 (t, *J* 6.9 Hz, 2 H), 7.25-7.30 (m, 3 H), 7.39-7.42 (m, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.5, 21.3, 22.2, 80.6, 90.2, 124.0, 127.4, 128.1 (2C), 131.5 (2C).

(*E*)-Dodec-3-en-1-ynylbenzene.[16] The title compound was prepared according to **Representative procedure A** except that phenylacetylene and (*E*)-1-iododecene were used instead of iodobenzene and 4-iodotoluene in the amount of Pd(DPEPhos)Cl$_2$ (100 μL, 10^{-4} M, 10^{-5} mmol). The reaction mixture was heated at reflux for 24 h, and the title compound was obtained in 70% GLC yield. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.89 (t, *J* 6.9 Hz, 3 H), 1.22-1.48 (m, 12 H), 2.12-2.20 (m, 2 H), 5.70 (dt, *J* 15.6, 1.8 Hz, 1 H), 6.20-6.31 (m, 1 H), 7.27-7.32 (m, 3 H), 7.40-7.45 (m, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.0, 22.6, 28.7, 29.1, 29.2, 29.4, 31.8, 33.2, 87.8, 88.3, 109.5, 123.6, 127.7, 128.1(2C), 131.3(2C), 145.1.

Hydrozirconation–Pd-catalyzed cross-coupling tandem reactions of alkynes with alkenyl bromides. **Representative procedure B. (2*E*,4*E*)-Ethyl undeca-2,4-dienoate.**[6] To a solution of ZrCp$_2$Cl$_2$ (438 mg, 1.5 mmol) in THF (4.5 mL) was added dropwise a solution of ^{i}Bu$_2$AlH (1.5 mL, 1.0 M solution in hexane, 1.5 mmol) at 0 °C in dark under argon atmosphere. After the resulting suspension was stirred at 0 °C for 30 min, a solution of 1-octyne (0.19 mL, 1.3 mmol) in THF (2 mL) was added, and the reaction mixture was warmed to 23 °C and stirred for 30 min. To a solution of ethyl (*E*)-ethyl 3-bromoacrylate (179 mg, 1.0 mmol) and PEPPSI-IPr (0.7 mg, 0.001 mmol) in THF (3 mL) was added the reaction mixture obtained above, and the resulting reaction mixture was stirred at 23 °C for 15 h. GC analysis indicated that the title compound was formed in 97% yield. The reaction mixture was quenched with water and extracted with ether. The combined organic layers were dried over anhydrous MgSO$_4$, filtered and concentrated. Flash chromatography (silica gel, 5% ethyl acetate in hexanes) afforded 192 mg (92%) of the title compound with ≥98% isomeric purity determined according to ^{1}H NMR. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.87 (t, *J* 7.0 Hz, 3 H), 1.20-1.39 (m, 9 H), 1.40-1.45 (m, 2 H), 2.16 (q, *J* 7.1 Hz, 2 H), 4.18 (q, *J* 7.0 Hz, 2 H), 5.77 (d, *J* 15.3 Hz, 1H), 6.05-6.22 (m, 2 H), 7.25 (dd, *J* 15.3, 10 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.0, 14.2, 22.5, 28.6, 28.8, 31.6, 32.9, 60.1, 119.1, 128.3, 144.7, 145.0, 167.2.

(2*Z*,4*E*)-Ethyl undeca-2,4-dienoate.[6] The title compound was prepared according to **Representative procedure B** except that (*Z*)-ethyl 3-bromoacrylate was used instead of (*E*)-ethyl 3-bromoacrylate. The reaction mixture was stirred at 23 °C for 15 h, and the title compound was obtained in 95% GLC yield. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.88 (t, *J* 7.0 Hz, 3 H), 1.20-1.50 (m, 11 H), 2.19 (q, *J* 7.1 Hz, 2 H), 4.18 (q, *J* 7.0 Hz, 2 H), 5.55 (d, *J* 11.4 Hz, 1 H), 6.07 (dt, *J* 15.3, 7.3 Hz, 1 H), 6.54 (t, *J* 11.1 Hz, 1 H), 7.31-7.41 (m, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.0, 14.2, 22.5, 28.7, 28.9, 31.6, 32.9, 59.7, 115.3, 126.8, 145.3, 145.7, 166.5.

[1,1'-biphenyl]-4-carbonitrile.[17] The title compound was prepared according to **Representative procedure A** except that 4-iodobenzonitrile was used instead of 4-iodotoluene. The reaction mixture was heated at reflux for 24 h, and the title compound was obtained in 83% GLC yield. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.46-7.51 (m, 3 H), 7.59-7.62 (m, 2 H), 7.68-7.74 (m, 4 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 110.5, 118.7, 126.9 (2C), 127.4 (2C), 128.4, 128.8 (2C), 132.3 (2C), 138.8, 145.2.

2-(4-nitrophenyl)thiophene.[18] To a solution of 1-iodo-4-nitrobenzene (100 mg, 0.4 mmol) and PEPPSI-IPent (0.3 mg, 4 × 10^{-4} mmol) in THF (1.5 mL) was added 2-thienylzinc bromide solution (1.12 mL, 0.5 M in THF, 0.56 mmol), and the resulting reaction mixture was stirred at 23 °C for 24 h. GC analysis indicated that the title compound was formed in 97% yield. The reaction mixture was quenched with water and extracted with ether. The combined organic layers were dried over anhydrous MgSO$_4$, filtered and concentrated. Flash chromatography (silica gel, 10% ethyl acetate in hexanes) afforded 76 mg (93%) of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.14 (dd, J 5.1, 3.9 Hz, 1 H), 7.43 (dd, J 5.1, 1.5 Hz, 1 H), 7.46 (dd, J 3.9, 1.5 Hz, 1 H), 7.71 (dt, , J 8.7, 2.4 Hz, 2 H), 8.21 (dt, , J 9.0, 2.4 Hz, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 124.3 (2C), 125.6, 125.8 (2C), 127.6, 128.6, 140.4, 141.4, 146.4.

Acknowledgements

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