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Domino Carbopalladation−Carbonylation: Generating Quaternary Stereocenters while Controlling β-Hydride Elimination

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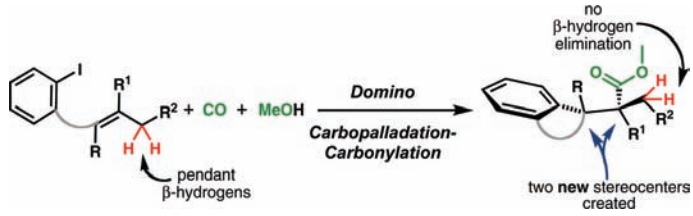
ABSTRACT



A domino carbopalladation−carbonylation sequence for substrates possessing β-hydrogens is explored. This allows for the construction of complex architectures with vicinal stereocenters in a concise and rapid fashion via the stereocontrolled formation of two carbon−carbon bonds. An integral aspect of this domino reaction is the ability to control β-hydride elimination of the organopalladium intermediate and instead form the carbonylation product.

The core scaffolds of numerous natural products and synthetic targets contain quaternary and vicinal stereocenters, which are challenging to construct even with current technology.[1] One reliable method for the assembly of such complex and congested architectures is the Heck reaction, of which even asymmetric variants are available.[2] An expansion of this method has led to "tandem Heck reactions", where via molecular queuing a second reaction sequence ensues subsequent to carbopalladation and prior to β-hydride elimination.[3] Despite the utility of such domino reactions, the substrates are often specifically engineered to avoid competitive β-hydride elimination, thus limiting the scope and applicability of such sequences.

Recent advances in the area of alkyl cross-coupling, as well as initial results in the trapping of organopalladium species, have led to an increased ability to control β-hydride elimination.[4] However, few of these methods address the construction of quaternary and vicinal stereocenters with *two* pendant hydrogens. We became interested, therefore, in designing a domino carbopalladation−carbonylation strategy aimed at the simultaneous construction of vicinal stereo-

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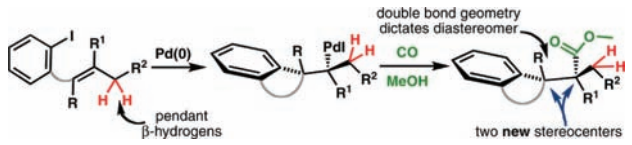
centers and two carbon−carbon bonds for substrates possessing β-hydrogens (Scheme 1).[5] In such a sequence, the

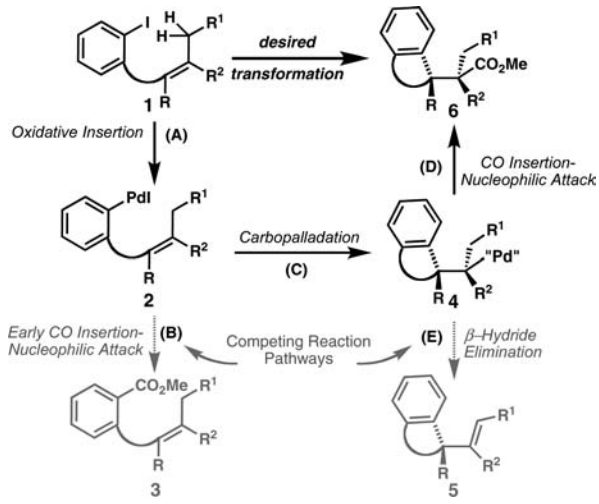
Scheme 1. Domino Carbopalladation−Carbonylation Strategy



organopalladium species derived from the initial carbopalladation event would be captured by CO instead of undergoing β-hydride elimination.[6] The benefits of this approach would be the rapid, stereospecific[7] synthesis of vicinal stereocenters for a new class of substrates, as well as the expeditious construction of complex architectures primed for further functionalization.

Central to the development of this transformation is the capacity to control the decomposition of the various organopalladium species, as there are several competing pathways that can transpire (Scheme 2). For example, after oxidative

Scheme 2. Pathways Available to the Organopalladium Species Where Alternatives Are Lettered A−E



insertion, the organopalladium **2** could be trapped by CO,[8] leading to the undesired ester **3** (arrow B). However, depending on the rate of cyclization, the organopalladium **2** can also undergo carbopalladation of the alkene, leading to organopalladium **4** (arrow C). This intermediate can then suffer decomposition via β-hydride elimination, yielding alkene **5** (arrow E), or intermediate **4** can be captured by CO, affording an acylpalladium species (arrow D). Nucleophilic attack on this acylpalladium species by methanol delivers the desired product **6** and regenerates the catalyst after loss of HI. Thus, careful examination of the desired transformation reveals several seemingly incongruent reactivity profiles. We postulated that we could dictate the course of the reaction by moderating the steric and electronic environment of the metal catalyst, as well as by modulating the CO pressure. The results of this endeavor are detailed below.

To prove our concept, we decided to focus our attention on the construction of 3,3-disubstituted oxindoles, a class of biologically important building blocks.[10] Model system **7** was chosen for this task, as the desired product **8** maps onto the core structures of the communesins[11] and perophoramidine, giving an advanced intermediate that would be cumbersome to construct as a single diastereomer via alternative routes.[12] This system would give alkene **9** in the case of the Heck reaction pathway (Scheme 2, arrows A, C, E) and ester **10** in the case of the early carbonylation pathway (Scheme 2, arrows A, B). We aimed to control the distribution of these three possible products.

The reaction was first tested at atmospheric pressure (Table 1, entry 1), but this produced only the Heck product **9** in 86% yield. We were delighted that by increasing the pressure to 100 psi with the same ligand 39% of the desired product **8** was obtained. However, there was also 24% of the Heck product **9** and 20% of the early ester product **10** (Table 1, entry 2). We experimented with both the palladium source and ligand and determined that dppf, 1,1′-bis(di-*tert*-butylphosphino)ferrocene, PCy_3, and P(2-furyl)$_3$ gave the best results (Table 1, entries 7−9 and 12). Since the mass balance was starting material with P(2-furyl)$_3$ as the ligand, we decided to focus our attention on improving this set of conditions, reasoning that finding the optimal solvent and

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(7) Assuming *syn* palladation.

(8) This acylpalladium species can then undergo carbopalladation, leading to further byproducts. For examples of carbonylation−carbopalladation−carbonylation sequences, see ref 3a for detailed outline.

(9) This acylpalladium species can then undergo carbopalladation, leading to further byproducts.

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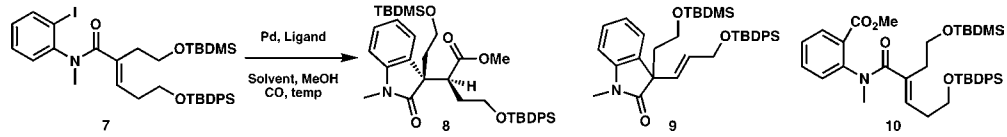
Table 1. Optimization of Domino Carbopalladation-Carbonylation for Amide **7**[a]



7 8 9 10

				yield (%)[c]		
entry	Pd source	pressure[b]	ligand	**8**	**9**	**10**
1	$Pd(OAc)_2$	atm	PPh_3		86	
2	$Pd(OAc)_2$	100	PPh_3	39	24	20
3	$Pd_2(dba)_3$•$CHCl_3$	100	$(t\text{Bu})_3PHBF_4$	14		18
4	$Pd_2(dba)_3$•$CHCl_3$	100	$SiMesHBF_4$[d]	24	7	14
5	$Pd(OAc)_2$	100	xanthphos[e]	9	5	5
6	$Pd(OAc)_2$	200	P(biphenyl)$(t\text{Bu})_2$	31	10	9
7	$Pd(OAc)_2$	100	dppf	50	9	11
8	$Pd(OAc)_2$	200	**11**	47		10
9	$Pd(OAc)_2$	100	PCy_3	50	25	17
10	$Pd(OAc)_2$	200	P(2-furyl)$_3$	31	10	10
11	$Pd_2(dba)_3$•$CHCl_3$	200	P(2-furyl)$_3$	44		17
12	$Pd_2(dba)_3$•$CHCl_3$	100	P(2-furyl)$_3$	45	4	17

[a] Reactions were run on 0.041 mmol scale of **7** in DMA and MeOH with 10 mol % of palladium (5 mol % in the case of $Pd_2(dba)_3$•$CHCl_3$) and 30 mol % of ligand and 4.4 equiv of Et_3N at the indicated pressure and 70 °C (internal temperature); **11** is 1,1′-bis(di-*tert*-butylphosphino)ferrocene. [b] Pressure in psi, prior to heating. [c] The yields (%) are from ^1H NMR of the crude product with 1-methoxynaphthalene as an internal standard. [d] 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate. [e] 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.

base combination could boost the reactivity but, as shown in the mechanism above, should not necessarily impact the product distribution.

Further optimization of the reaction parameters included determining the optimal solvent and base. The solvent screen revealed that DMA was the best solvent.[13] A variety of bases were then examined, showing that solid bases were not effective (Table 2, entry 4). A clear relationship between basicity and reaction yield was also not observed (Table 2).[14] An improvement of the conditions and complete consumption of starting material was seen with DMAP; however, 28% of a new side product **12** was also detected under these conditions. Regioisomer **12** presumably arises from β-hydride elimination followed by reinsertion of the Pd−H into the coordinated alkene and then trapping of this resultant organopalladium with CO. We hypothesized that this was due to the inability of DMAP to reduce the Pd−H intermediate to Pd(0). To retain the reactivity seen with the DMAP while minimizing the formation of **12**, we opted to use a catalytic amount of DMAP in conjunction with a stoichiometric base to reduce the Pd−H intermediate (Table 2, entries 8 and 9). Using DABCO as the stoichiometric base gave the desired effect, minimizing the formation of **12**, while increasing the formation of ester **8**.

Table 2. Optimization of Base for the Domino Carbopalladation−Carbonylation of Amide **7**[a]

		yield (%)[b]			
entry	base	**8**	**9**	**10**	**12**
1	Et_3N	45	4	17	
2	DBU	22	10	17	
3	DABCO	38	4		
4	Cs_2CO_3	9	13	19	
5	TMG	23	6		
6	Cy_2NMe	40	10		
7	DMAP	51	4		28
8	DMAP + Et_3N	27	8	6	7
9	DMAP + DABCO	55	8	8	6

[a] Reactions were run on 0.041 mmol scale in DMA and MeOH with 5 mol % of $Pd_2(dba)_3$•$CHCl_3$ and 30 mol % of P(2-furyl)$_3$ and 4.4 equiv of the indicated base at 100 psi and 70 °C (internal temperature). Entries 9 and 10, 0.4 equiv of DMAP and 4 equiv of alternative base. Remainder of mass balance is starting material. [b] The yields (%) are from ^1H NMR of the crude product with 1-methoxynaphthalene as an internal standard.

With these optimized conditions in hand, we then explored the scope of this transformation. The performance of the reaction is highly dependent on the N-protecting group, as the unprotected amide yields products related only to early esterification (Table 3, entry 2).[15] Increasing the steric bulk of the protecting group to a 4-CF_3 benzyl group resulted in an improved yield (entries 1 and 3). Surprisingly, use of a 4-MeO-substituted benzyl group gave identical yields, implying that this is purely a steric effect (entry 4). These results indicate that a larger protecting group amplifies the rate of carbopalladation and suppresses the formation of the early esterification product. The protecting groups also minimized the formation of the β-hydride elimination/

(13) See Supporting Information for further details.

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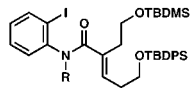
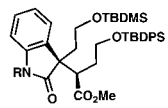
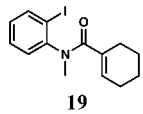
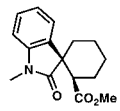
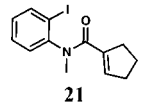
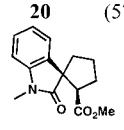
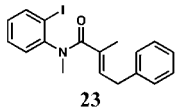
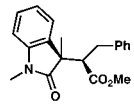
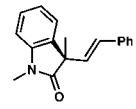
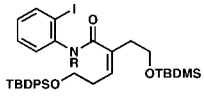
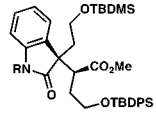
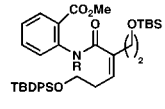
Table 3. Scope of the Domino Carbopalladation−Carbonylation Sequence[a]

entry	substrate	product/(yield[b])	byproduct/(yield)[b]
			
1	R = Me, **7**	R= Me, **8** (50)	See Table 2
2	R= H, **13**	R= H, **14** (0)	-
3	R= *p*-CF_3 $C_6H_4CH_2$, **15**	R= *p*-CF_3 $C_6H_4CH_2$, **16** (69)	-
4	R= *p*-MeO $C_6H_4CH_2$, **17**	R= *p*-MeO-$C_6H_4CH_2$, **18** (69)	-
5	 **19**	 **20** (57)	-
6	 **21**	 **22** (67)	-
7	 **23**	 **24** (40)[c]	 **25** (40)
			
8	R = Me, **26**	R= Me, **27** (40)	R= Me, **28** (35)
9	R= *p*-MeO $C_6H_4CH_2$, **29**	R= *p*-MeO $C_6H_4CH_2$, **30** (51)	R= *p*-MeO $C_6H_4CH_2$, **31** (34)

[a] Reactions were run on 0.08 mmol scale in DMA and MeOH with 5 mol % of $Pd_2(dba)_3$•$CHCl_3$ and 30 mol % of P(2-furyl)$_3$ and 4 equiv of DABCO and 0.4 equiv of DMAP at 100 psi (prior to heating) and 70 °C (internal temperature). [b] Isolated yields. [c] With 7% of ester isomer from reinsertion also isolated.

reinsertion product corresponding to ester **12**, which is unexpected based on the mechanism. Two bicyclic systems were constructed with good yields under these conditions (entries 5 and 6). The selectivity of the esterification reaction was reduced, with an aryl substituent α to the olefin as we isolated both the corresponding Heck product **25**, as well as the isomeric ester product arising from a β-hydride elimination/reinsertion process (entry 7). This lowered selectivity was expected as the aryl moiety allows for more facile β-hydride elimination. We also examined the use of the *Z* double bond isomers **26** and **29** (entries 8 and 9), which showed reduced reactivity, yet followed same protecting group trend. Interestingly, none of the reinsertion product nor the β-hydride elimination product was observed for these cases. However, approximately 35% of the early carbonylation product was isolated. Ideally, this reaction should be examined for tetrasubstituted olefins, and currently, this is under investigation in our laboratory.

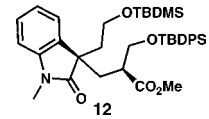

12

Figure 1. Byproduct observed with DMAP as base.

In conclusion, we have developed a domino carbopalladation−carbonylation process that allows substrates to possess β-hydrogens, resulting in the stereospecific formation of two new carbon−carbon bonds. This novel sequence not only expands the scope of the traditional carbonylation reactions but also provides valuable information on our ability to dictate the fate of an organopalladium intermediate. We hope to apply this rationale to new reaction manifolds, allowing for greater diversity in palladium-catalyzed reactions.

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Supporting Information Available: Detailed experimental procedures and spectra reported for compounds **8**−**10** and **12**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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