Carbonylation

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Cooperative Strategy for the Highly Selective Intermolecular Oxycarbonylation Reaction of Alkenes using Palladium Catalyst

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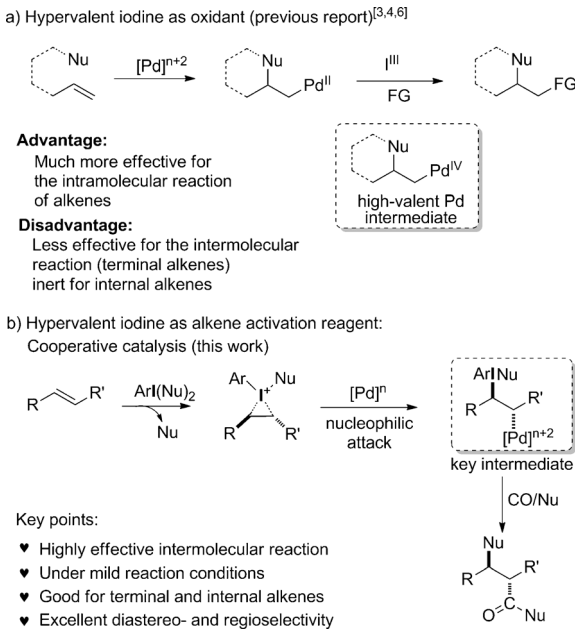
Dedicated to Prof. Qilin Zhou on the occasion of his 60th birthday

Abstract: *A novel method for intermolecular functionalization of terminal and internal alkenes has been designed. The electrophilic reagent, hypervalent iodine, plays a key role in this process by activating the alkene C=C bond for nucleophilic addition of the palladium catalyst. This process generates an iodonium-containing palladium species which undergoes CO insertion. The new approach, intermolecular oxycarbonylaton reactions of alkenes, has been achieved and carried out under mild reaction conditions to produce the corresponding β-oxycarbonylic acids with excellent efficiencies and levels of regio- and diastereoselectivity.*

The development of methods to carry out highly selective functionalization reactions of alkenes is important in the context of organic synthesis.[1] Owing to their high level of step economy, difunctionalization reactions of alkenes (DFAs) are synthetically attractive.[2] In the last decade, numerous high-valent palladium catalyzed processes, in which hypervalent iodine reagents are commonly used as oxidants, have been developed as efficient approaches to carry out DFAs (Scheme 1 a).[3,4] However, in contrast to the highly efficient intramolecular versions, the intermolecular counterparts of these DFAs are often not as effective. Furthermore, as a result of their sterically hindered nature, internal alkenes are difficult to activate by palladium catalysts and, consequently, they are much less reactive and/or undergo undesired alkene isomerization reactions.[5] For instance, we recently described a palladium-catalyzed intermolecular aminocarbonylation reaction of terminal alkenes and it serves as one of most efficient approaches to the synthesis of β-aminoacids. However, internal alkenes are completely inert under the reaction conditions employed for reactions of their terminal counterparts.[6] Thus, studies aimed at uncovering new methods to promote intermolecular DFAs have a synthetic significance.

Iodine(III) reagents have been employed broadly to activate both terminal and internal alkenes.[7] Unfortunately, compared to the diverse reactivity profiles of organometallic complexes of alkenes, iodine(III)-mediated reactions are thus far limited to nucleophilic substitution processes. We surmised that a strategy, which utilizes transition-metal (TM) catalysts to promote nucleophile addition to activated C=C bonds, would be a key component in the design of new DFAs.[8,9] In processes promoted in this manner, a new type of organometallic species would serve as a key intermediate. Thus, it should be possible to use this strategy to design new transformations. To our knowledge, reactions of this type have not been explored previously. One unique feature of organometallic complex is their ability to participate in rapid CO insertion reactions which generate carbonyl compounds.[10] Importantly, this process does not occur in typical iodine(III)-mediated/catalyzed reactions when TM catalysts are absent or in alkene reactions promoted by TM catalysts alone.[7] In studies designed to test the feasibility of the new strategy, we uncovered a novel cooperative transition-metal and iodine(III)-mediated activation mode which serves as the basis for efficient and selective intermolecular β-oxycarbonylation of both terminal and internal alkenes (Scheme 1 b).

The β-oxycarboxylic acid motif is an important core structure in natural products, pharmaceuticals, and biomaterials.[11] At the outset of the current effort, we speculated that



Scheme 1. Palladium-catalyzed difunctionalization reaction of alkenes. FG = functional group.

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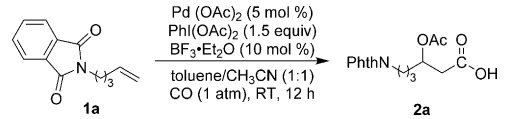
a three-membered-ring iodonium intermediate, formed from $PhI(OAc)_2$ and alkenes, might react with a TM catalyst in the presence of CO to produce oxycarboxylic acids. To test this proposal, the terminal alkene, phthalimido-pentene **1a** (see Table 1), was subjected to a reaction promoted by a palladium catalyst and $PhI(OAc)_2$. The results show that intermolecular acetoxycarbonylation of the alkene occurs to form the β-oxycarboxylic acid **2a**. An extensive screen of reaction parameters (Table 1) led to optimized reaction conditions

Table 1: Optimization of the reaction conditions for reaction of **1a** to form **2a**.[a]



Entry	Reaction conditions	Yield [%][b]
1	"Standard conditions"	95 (90,[c] 71[d])
2	$[Pd(dba)_2]$ instead of $Pd(OAc)_2$	86
3	$[Pd(PPh_3)_4]$ instead of $Pd(OAc)_2$	0
4	no Pd catalyst	0[e]
5	$Cu(OAc)_2$ instead of $PhI(OAc)_2$	0
6	no $BF_3{\cdot}Et_2O$	0[e]
7	N_2 atmosphere (without CO)	0[e]
8	$Zn(OTf)_2$ instead of $BF_3{\cdot}Et_2O$	72
9	$Mg(ClO_4)_2$ instead of $BF_3{\cdot}Et_2O$	68
10	$Yb(OTf)_3$ instead of $BF_3{\cdot}Et_2O$	44
11	HOTf instead of $BF_3{\cdot}Et_2O$	79
12	$PhI(O_2CCF_3)_2$ instead of $PhI(OAc)_2/BF_3{\cdot}Et_2O$	74[f] (79)[f,g]

[a] Reaction conditions: all reactions were run at 0.2 mmol scale. [b] Yield as determined by ^1H NMR spectroscopy using CF_3-DMA as an internal standard. Regioselectivities in all case are above 20:1. [c] $Pd(OAc)_2$ (2 mol%). [d] $Pd(OAc)_2$ (1 mol%). [e] Olefin **1a** was recovered nearly quantitatively. [f] β-trifluoroacetoxyl carboxylic acid as product. [g] $Pd(O_2CCF_3)_2$ (5 mol%) was used as catalyst. dba = dibenzylideneacetone, DMA = dimethylacetamide, HOTf = trifluoromethanesulfonic acid.

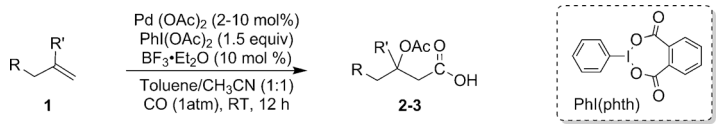
for this process, and involves the use of $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (1.5 equiv), $BF_3{\cdot}OEt_2$ (10 mol%), toluene and acetonitrile (v/v = 1:1) as the solvent and under a CO atmosphere (1 atm) at room temperature. Under these reaction conditions, **1a** forms **2a** in an excellent yield (95%) and regioselectivity (entry 1). Moreover, the use of $[Pd(dba)_2]$ in place of $Pd(OAc)_2$ to promote this process gives similar results (entry 2), but **2a** is not generated when $[Pd(PPh_3)_4]$ is utilized as the catalyst (entry 3). The results of control experiments revealed that the palladium catalyst, $PhI(OAc)_2$, $BF_3{\cdot}OEt_2$, and CO gas are all required for this reaction to occur (entries 4–7).

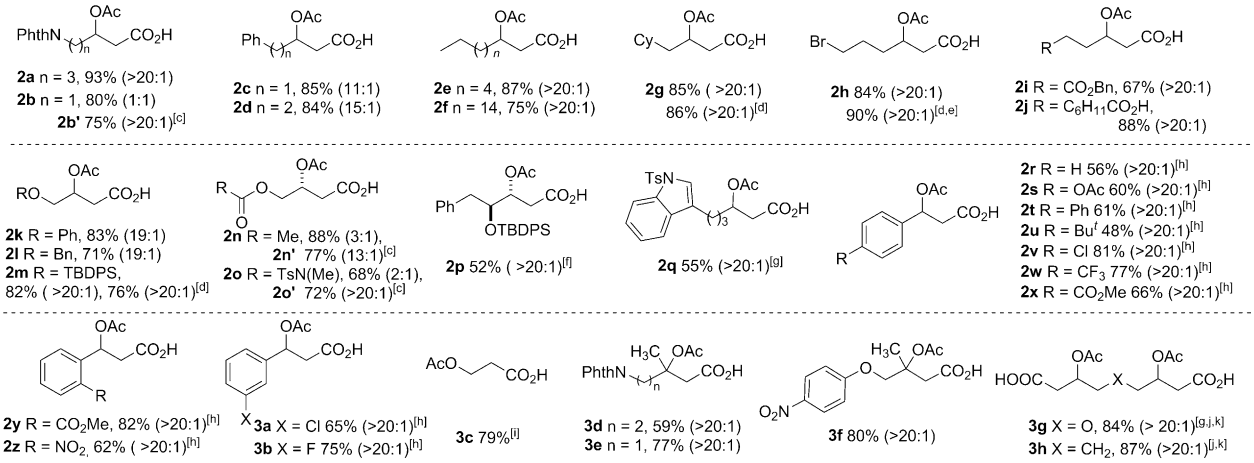
We reasoned that the role played by $BF_3{\cdot}OEt_2$ in this DFAs is to activate loss of acetate from $PhI(OAc)_2$, thus producing the cationic $PhI(OAc)^+$ species which reacts with the alkene to form the three-membered iodonium ion intermediate. Although reaction takes place when other Lewis and Brønsted acids are utilized, the highest yield is obtained when $BF_3{\cdot}OEt_2$ serves as the promoting agent (Table 1, entries 8–11). However, $BF_3{\cdot}OEt_2$ is not required when $PhI(O_2CCF_3)_2$ is employed to promote this reaction (entry 12). In addition, use of acetonitrile as a co-solvent is necessary for the success of the transformation, likely because this nitrile stabilizes and/or increases the nucleophilicity of the palladium species. Finally, it is possible to lower the palladium catalyst loading and still maintain the efficiency of the reaction (e.g., 90% yield with 2 mol% Pd catalyst, and 71% yield with 1 mol%; entry 1).

With the optimized reaction conditions in hand, our attention turned to an exploration of the substrate scope with respect to the alkene. The results (Table 2) show that aliphatic terminal alkenes react efficiently to yield the corresponding acids **2a**–**q**. A number of functional groups, including ethers, esters, carboxylic acids, imides, halides, and indoles, remain unchanged under the reaction conditions. Noteworthy, excellent levels of regioselectivity, corresponding to addition of the acetoxy and carboxylate groups to the respective internal and terminal alkene carbon atoms, result from these reactions. Exceptions to this trend are seen when substrates containing chelating allylic ester and amide groups are used, as exemplified by reactions that form **2b**, **2n**, and **2o** with poor levels of regioselectivity (1–3:1). Interestingly, the regioselectivities for formation of these adducts are dramatically improved when $PhI(OAc)_2$ is replaced by PhI(phth) (>20:1 for **2b** and **2o**, and 13:1 for **2n**). Also, reaction of the *t*-butyldiphenylsilyl-protected allylic alcohol forms **2p** in 52% yield with greater than 20:1 regioselectivity and 7:1 diastereoselectivity for the *anti* isomer. Furthermore, reactions of styrene derivatives bearing functional groups on the arene ring were also surveyed. Under the optimized reaction conditions with $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (2.5 equiv), $BF_3{\cdot}OEt_2$ (20 mol%), and toluene and acetonitrile (v/v = 9:1) as the solvent, these reactions generate the desired products **2r**–**3b** in high yields and excellent regioselectivities (>20:1). Ethylene gas also reacts to form the expected product **3c** in 79% yield. Selected 1,1-disubstituted alkenes also serve as good substrates for the acetoxycarbonylation reaction, thus producing **3d**–**f** as single isomers in good yields. Interestingly, nonconjugated dienes react under the optimized reaction conditions to form the bis-acetoxycarbonylation products **3g**,**h**, processes that differ from previously explored carbonylation reactions of dienes.[12] Importantly, the reaction can be extended to a 5 mmol scale by using 2 mol% $Pd(OAc)_2$, as exemplified by the generation of **2h** in high yield (90%). In the large-scale reaction, the side product PhI can be recovered in over 95% yield and readily reoxidized by H_2O_2 to produce $PhI(OAc)_2$ in quantitative yield.

Our attention next turned to assessing the reactivities of internal alkenes (Table 3). The results of a preliminary study showed that the reactivity of (*E*)-4-octene [(*E*)-**4a**] is significantly lower than those of terminal alkenes. However, this substance undergoes the reaction to form *anti*-**5a** in high yield (86%) and with an excellent level of diastereoselectivity (>20:1) when a palladium catalyst loading of 10 mol% is utilized. Interestingly, the opposite diastereoisomer, *syn*-**5a**, is selectively generated in 72% yield when (*Z*)-4-octene [(*Z*)-**4a**] is employed as the substrate. Other symmetric alkenes, such as **4b**–**d**, exhibit the same level of reactivity and undergo the process to form the corresponding products **5b**–**d** efficiently with excellent diastereoselectivities. Reactions of asymmetric alkenes also give the corresponding products **5e**–

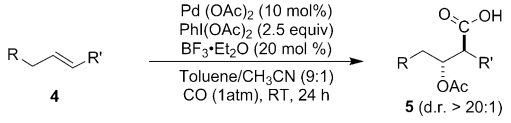
Table 2: Substrate scope with respect to alkenes.[a,b]

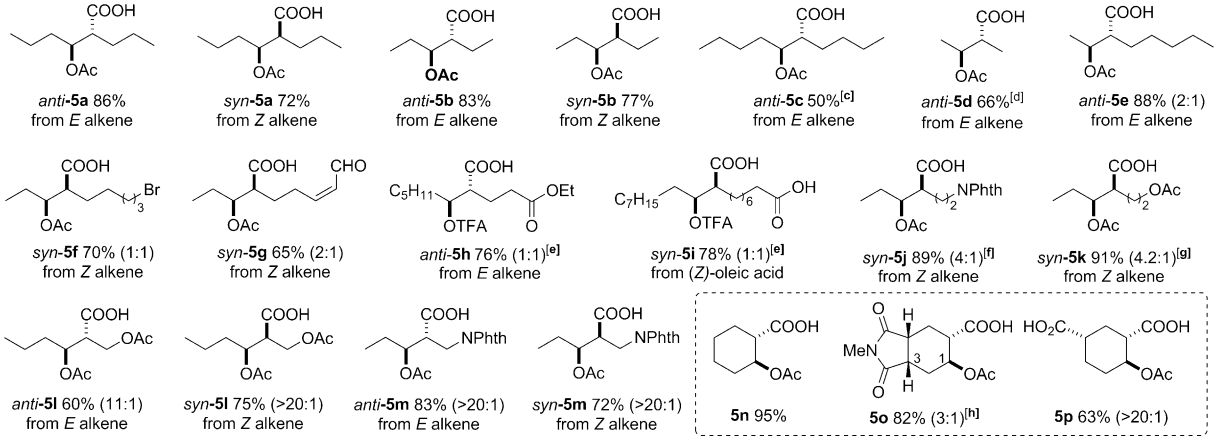




[a] Reaction conditions: substrate 1 (0.2 mmol), $Pd(OAc)_2$ (5 mol %), BF_3 Et_2O (10 mol %), $PhI(OAc)_2$ (1.5 equiv) in CH3CN/toluene (1 mL, v/v = 1:1) at room temperature under CO balloon. [b] Yield of isolated product. The value within parentheses is that of the regioselectivity. [c] PhI(phth) instead of $PhI(OAc)_2$, product **2b′**, **2n′**, and **2o′**: OAc replaced by O_2CAr (Ar = *o*-$C_6H_4CO_2H$). [d] $Pd(OAc)_2$ (2 mol%). [e] Run on a 5 mmol scale with 95% PhI recovered. [f] d.r. = 7:1. [g] $Pd(OAc)_2$ (10 mol %). [h] $Pd(OAc)_2$ (10 mol %), BF_3 Et_2O (20 mol %), $PhI(OAc)_2$ (2.5 equiv) in CH_3CN/toluene (1 mL, v/v = 1:9). [i] $PhI(OAc)_2$ as a limiting reagent. [j] $PhI(OAc)_2$ (3 equiv). [k] d.r. = 1:1. TBDPS = *tert*-butyldiphenylsilyl, Ts = 4-toluenesulfonyl.

Table 3: Substrate scope with respect to internal alkenes.[a,b]





[a] Reaction conditions: Substrate **4** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), BF_3 Et_2O (20 mol %), $PhI(OAc)_2$ (2.5 equiv) in CH_3CN/toluene (v/v = 1:9, 1 mL) at room temperature with CO balloon. [b] Yield of isolated product. The d.r. value is over 20:1 in all cases, and the value within parentheses is that of the regioselectivity. [c] $[Pd(CH_3CN)_4](OTf)_2$ as the catalyst. [c] $PhI(OAc)_2$ was used as a limiting reagent. [e] With $Pd(O_2CCF_3)_2$/$PhI(O_2CCF_3)_2$ system. [f] *p*-$MeC_6H_4I(OAc)_2$ (2.5 equiv) instead of $PhI(OAc)_2$. [g] 3,5-$Me_2C_6H_3I(OAc)_2$ (2.5 equiv) instead of $PhI(OAc)_2$. [h] The d.r. ratio for 1,3 positions. TFA = trifluoroacetyl.

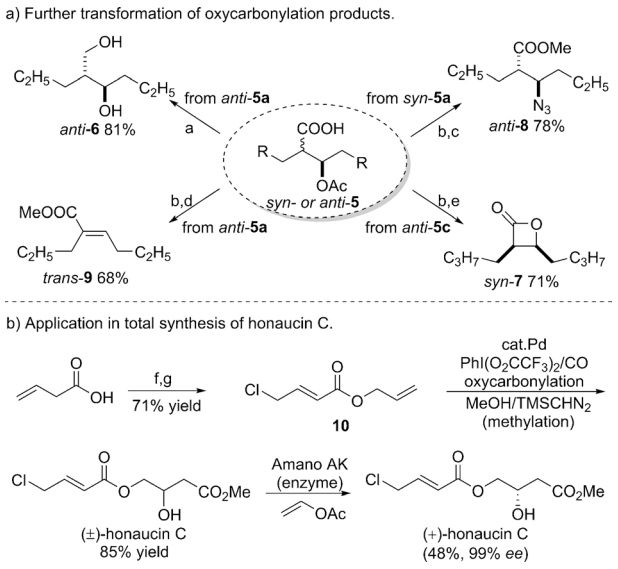
i with excellent levels of diastereoselectivity (> 20:1) but poor (1–2:1) regioselectivities. Interestingly, the substrate (*Z*,*Z*)-**4g**, bearing both electron-rich and electron-deficient internal alkene moieties, undergoes the acetoxycarboxylation reaction (65 %) at only the electron-rich alkene center to form *syn*-**5g**. In addition, commercially available ethyl (*E*)-3-nonenate and (*Z*)-oleic acid, both of which contain long alkyl chains, react when treated with the $PhI(OCCF_3)_2$/$Pd(O_2CCF_3)_2$ system to form the respective products *anti*-**5h** and *syn*-**5i** in good yields.

It was interesting to find that introduction of a chelating group enables control of the regioselectivity of this process. For example, the homoallylic phthalimide and acetate groups in the alkenes (*Z*)-**4j** and (*Z*)-**4k** direct the acetoxycarboxylation reaction to form the products *syn*-**5j** and *syn*-**5k**, respectively, predominantly (ca. 4:1), wherein carboxylate moiety is vicinal to the directing groups. Moreover, these allylic directing groups in alkenes (*E*)/(*Z*)-**4l** and (*E*)/(*Z*)-**4m** enhance the regioselectivity (11:1 and > 20:1, respectively) of reactions that generate *anti/syn*-**5l** and *anti/syn*-**5m**, respectively. Cyclohexenes **4n** and **4o** also serve as good substrates for this process and form *anti*-**5n** (95%) and *anti*-**5o** (82%), respectively. Surprisingly, reaction of **4p**, where the imide group in **5o** is replaced by a carboxylic acid moiety, takes place efficiently (63%) to give **5p** with excellent levels of regio- and diastereoselectivity. This observation suggests that coordination of a carboxylic acid group with palladium in the catalyst enhances the step in the process in which it serves as a nucleophile. Notably, being distinctly different from previous TM catalyzed functionalization reactions of internal alkenes,[5] the reaction developed in the current study generates only trace amounts of alkene isomerization products.

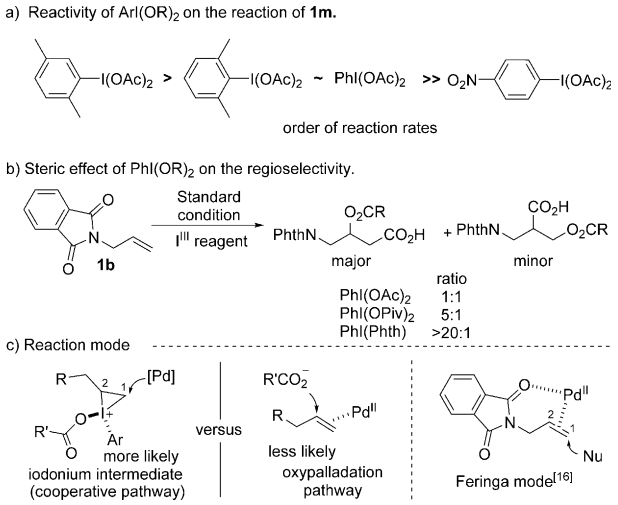
Because the new DFAs is highly efficient, we believed it would be worthwhile to explore and utilize reactions of the generated β-oxycarboxylic acid products. As shown by the examples displayed in Scheme 2a, these substances are readily converted into 1,3-diols (*anti*-**6**), β-lactones (*syn*-**7**), β-azido esters (*anti*-**8**), and α,β-unsaturated alkenes (*trans*-**9**) with excellent levels stereoselectivity and in good yields.

A specific example demonstrating the preparative potential of the new β-oxycarboxylation method is its use in the preparation of (+)-honaucin C (Scheme 2b). To our knowledge, no approach has yet been described for the synthesis of this natural product, which is isolated from the bloom-forming cyanobacterium Leptolyngbya crossbyana, and displays anti-inflammatory and quorum-sensing inhibitory properties.[13] The plan we employed to prepare honaucin C begins with 3-butenoic acid, which is transformed into the allylic ester **10** by sequential chlorination and esterification. Importantly, oxycarbonylation reaction of **10** occurs exclusively at the terminal alkene center, even though allylic chlorides like those present at the other center are reactive in palladium(0)-catalyzed processes.[14] The high chemoselectivity of the reaction of **10**, a substance containing an array of sensitive functional groups, demonstrates the synthetic power of the new process. Finally, methylation using methanol and $TMSCHN_2$ produces racemic honaucin C in four linear steps and an overall 60% yield. Importantly, enantiomerically pure (+)-honaucin C can be generated from the racemate using enzymatic kinetic resolution with Amano AK.

Finally, some experiments were conducted to gain information about the mechanism. The steric and electronic effects of the iodine(III) reagent were initially explored. The results show that less sterically hindered and electron-rich iodine(III) reagent exhibited faster reaction rate than more sterically crowded and electron-deficient iodine(III) reagent (Scheme 3a).[15] Secondly, reaction of the allylimide **1b**, which contains a chelating group, provided **2b** predominantly with various iodine(III) reagents (Scheme 3b). The observations summarized above suggest that the β-oxycarboxylation process is possibly initiated by formation of a three-membered iodonium ion, which is stabilized by electron-rich substituents on the positively charged iodine center, and the nucleophilic attack of iodonium by palladium is retarded by the stereic hindrance of aryl ring (Scheme 3c, left). For the alternative oxypalladation and sequential CO insertion pathway (Scheme 3c, middle), several observations suggest that it is less likely: 1) the iodine(III) reagent in this mechanistic route would merely serve as an oxidant to regenerate Pd^{II} from Pd^0. Thus, owing to their stronger oxidizing ability, electron-withdrawing-substituted iodine(III) reagents would favor Pd^{II} regeneration and perhaps accelerate the process. This pre-



Scheme 2. Selected transformations and synthetic applications. Reaction conditions: a) $LiAlH_4$, THF, reflux. b) K_2CO_3, MeOH, RT; c) PPh_3, DIAD, $Ph_2P(O)N_3$, THF, 0°C–RT. d) PPh_3, DIAD, THF, 0°C–RT. e) $PhSO_2Cl$, pyridine, 0°C–RT. f) PhSeCl, NCS. g) Allylic alcohol, DCC.



Scheme 3. Preliminary mechanistic investigation.

diction is opposite to the observation; 2) the typical chelating effect on the nucleopalladation reaction of **1b** causes it to favor the C1 position, as proposed by Feringa (Scheme 3c, right),[16] and result in predominant formation of the opposite regioisomer to **2b**; 3) oxypalladation processes typically favor electron-deficient alkenes,[17] whereas the iodine(III)-mediated reactions take place selectively at electron-rich alkene centers.[7] The selective formation of *syn*-**5g** (Table 3) and honausin C (Scheme 2b) exemplifies this significant difference.

In summary, we have developed a novel synergestic, transition-metal-catalyzed and iodine(III)-mediated, DFAs for β-oxycarboxylation, and both terminal and internal alkenes participate. The process, which is conducted under very mild reaction conditions, has good functional-group compatibility, broad substrate scope, and high levels of regio- and diastereoselectivity. The new oxycarbonylation process serves as an efficient method for bis-functionalization of alkenes. Given the importance of the β-hydroxycarboxylic acid core structure in nature products, pharmaceuticals and biomaterials, this method should find wide applications in organic synthesis.

Acknowledgements

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Keywords: alkenes · carbonylation · iodine · palladium · total synthesis

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Communications

Carbonylation

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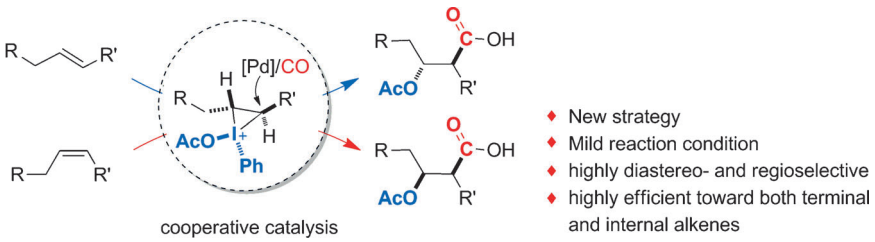
Cooperative Strategy for the Highly Selective Intermolecular Oxycarbonylation Reaction of Alkenes using Palladium Catalyst



'**Kene activation**: A novel method for intermolecular oxycarbonylation of terminal and internal alkenes has been designed. The electrophilic reagent, hypervalent iodine, plays a key role in this process by activating the alkene bond for nucleophilic addition of the palladium catalyst.