Zitierweise: *Angew. Chem. Int. Ed.* **2021**, *60*, 17693 – 17700
Internationale Ausgabe: doi.org/10.1002/anie.202105977
Deutsche Ausgabe: doi.org/10.1002/ange.202105977

Homogeneous Catalysis

Asymmetric Alkoxy- and Hydroxy-Carbonylations of Functionalized Alkenes Assisted by β-Carbonyl Groups

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Dedicated to Professor Matthias Beller on the occasion of his 60th birthday

Abstract: *As a fundamental type of carbonylation reaction, the alkoxy- and hydroxy-carbonylation of unsaturated hydrocarbons constitutes one of the most important industrial applications of homogeneous catalysis. However, owing to the difficulties in controlling multi-selectivities for asymmetric hydrocarbonylation of alkenes, this reaction is typically limited to vinylarenes and analogues. In this work, a highly efficient asymmetric alkoxy- and hydroxy-carbonylation of β-carbonyl functionalized alkenes was developed, providing practical and easy access to various densely functionalized chiral molecules with high optical purity from broadly available alkenes, CO, and nucleophiles (>90 examples, 84–99% ee). This protocol features mild reaction conditions and a broad substrate scope, and the products can be readily transformed into a diverse array of chiral heterocycles. Control experiments revealed the key role of the β-carbonyl group in determining the enantioselectivity and promoting the activity, which facilitates chiral induction by coordination to the transition metal as rationalized by DFT calculations. The strategy of utilizing an innate functional group as the directing group on the alkene substrate might find further applications in catalytic asymmetric hydrocarbonylation reactions.*

Introduction

Transition-metal-catalyzed carbonylation reactions are fundamentally important homogeneous catalysis process.[1] Of growing importance are alkoxy- and hydroxy-carbonylations, which can convert unsaturated hydrocarbons to backbone-elongated carboxylic acid derivatives with carbon monoxide (CO) and nucleophiles. This reaction is characterized by perfect atom-economy, and has achieved numerous industrial-scale applications.[2] Since the birth of asymmetric catalysis,[3] the enantioselective hydrocarbonylation has been recognized as one of the most direct and efficient methods for the preparation of optically active carbonyl compounds.[4] Despite extensive efforts, however, this reaction is generally plagued by difficult control of multi-selectivities (chemo-, site- and stereoselectivities) as well as harsh reaction conditions (elevated temperature and high CO gas pressure). For the carbonylation of alkenes without aryl-substituent, the alkyl-palladium intermediate readily undergo reversible β-hydride elimination and insertion, leading to isomerization of the double bonds and a mixture of olefins. Although this intrinsic reactivity has been extensively exploited for the synthesis of linear esters from internal/mixed alkenes with CO and alcohols,[5] this renders the asymmetric hydrocarbonylation of common olefins a daunting challenge. Therefore, so far the scope of this reaction is typically limited to vinylarenes[6] and analogues (Scheme 1, a and b).[7]

Precoordination of a transition-metal with functional groups (FGs) in substrates has been exploited to control stereoselectivity and promote reactivity in asymmetric catalytic reactions including hydrogenation,[8] epoxidation[9] and C–H bond functionalization.[10] With this in mind, we envisioned that the multi-selectivity issues in asymmetric hydrocarbonylation of multi-substituted alkenes could be alleviated by introducing a FG into the proper position on olefinic substrate (Scheme 1, c).[11] It was anticipated that the FG may act as a directing group (DG), which by coordination to the transition-metal would guide the insertion of the unsaturated bond to palladium-hydride at the privileged position, and may inhibit β-hydride elimination through the formation of a more rigid palladacycle. In this way, multi-site interaction between the catalyst and the substrate would facilitate chiral induction in the asymmetric carbonylation process. It is generally accepted that an appropriate DG should coordinate to the metal not too strong to outcompete ligands for vacant coordination sites, which could be detrimental for asymmetric catalysis as these background reactions erode enantioselectivity. An innate FG in the alkene would be preferable, as the FG might be advantageously utilized in further reactions by simple functional group interconversion (FGI). Recent seminal studies have demonstrated that by employing simple and commonly encountered functional groups as the coordination sites, the weak coordination between the substrate and the metal center of catalysts can prompt the reactivity and control the chemo- and stereoselectivities. Therefore, we turn our attention to using weakly coordinating groups, such as carbonyl groups typically found in ketone and carboxylic acid derivatives, as the DGs. These moieties represent one sort of the most versatile handles for further synthetic manipulations, and can be readily transformed into a diverse range of other functionalities.[12] Herein,

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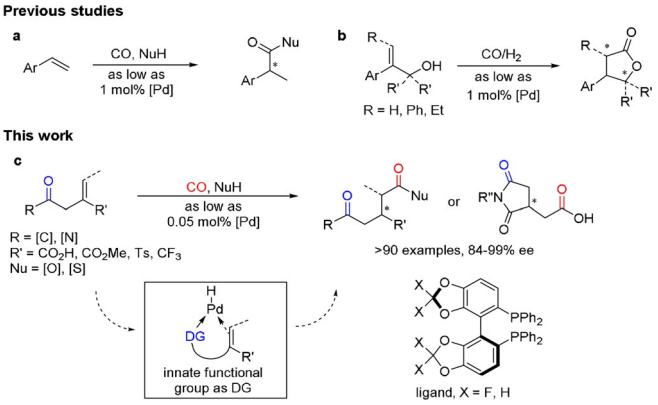


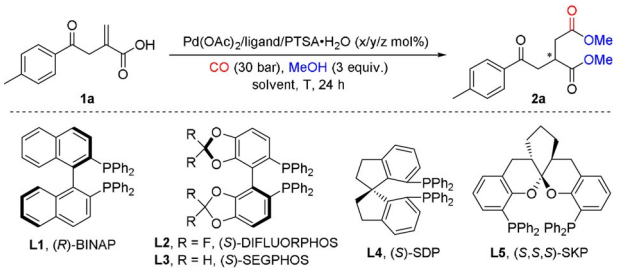
Scheme 1. Asymmetric catalytic alkoxy- and hydroxy-carbonylations.

we reported a highly efficient asymmetric alkoxy- and hydroxy-carbonylations of β-carbonyl functionalized alkenes, wherein the carbonyl group as the DG was demonstrated to be crucial for controlling the chemo- and stereoselectivities, and favorable for catalytic activities (Scheme 1, c). Such protocol provided a practical and ready access to various chiral densely functionalized molecules with high optical purity (>90 examples, 84–99% *ee*) from alkenes, CO, and nucleophiles. The reactions were typically performed at ambient temperatures and tolerated different nucleophiles (alcohols, water and thiol). Monitoring reaction profiles, control experiments and DFT calculation confirmed the key role of the carbonyl group in determining the stereoselectivity, while the presence of an electron-withdrawing vinyl substituent (e.g., -CO_2H, -CO_2Me, -Ts, -CF_3) could effectively inhibit the alkene isomerization via the tertiary carbocation intermediates.

Results and Discussion

To examine the feasibility of this idea, α-methylene-γ-keto carboxylic acid **1a** was selected as the benchmark substrate for the asymmetric methoxycarbonylation, and some privileged bidentate phosphines were screened as chiral ligands (Table 1). The reaction was carried out under 30 bar CO in MeOH at 60 °C for 24 h, with the in situ generated $Pd(OAc)_2$-(*R*)-BINAP (**L1**)-PTSA·H_2O catalyst system. Gratifyingly, the desired product **2a** was obtained with 70% enantiomeric excess (*ee*) and 82% GC yield (Table 1, entry 1). After varying the reaction solvent, the *ee* value was improved to 87% in toluene with 3 equiv of MeOH (entry 3). Subsequently, chiral ligands **L2**–**L5** were investigated in this reaction (entries 5–8), and (*S*)-DIFLUORPHOS (**L2**) turned out to be optimal, giving **2a** with excellent activity and enantioselectivity (entry 5, for the effect of more ligands, see Table S1 in SI). Further optimization of other reaction parameters including temperature and catalyst loading (entries 9–12) demonstrated that such methoxycarbonylation preceded well even at 40 °C or rt (entries 11 and 12). Notably, reducing the palladium catalyst loading to 0.2 mol% could still afford **2a** with 86% yield and 94% *ee* on gram-scale (entry 13). Using the corresponding methyl ester of **1a** as the substrate for the enantioselective methoxycarbonylation gave lower yield and *ee* value of **2a** compared with that using substrate **1a** (entries 14 and 15 versus 5 and 11, respectively).

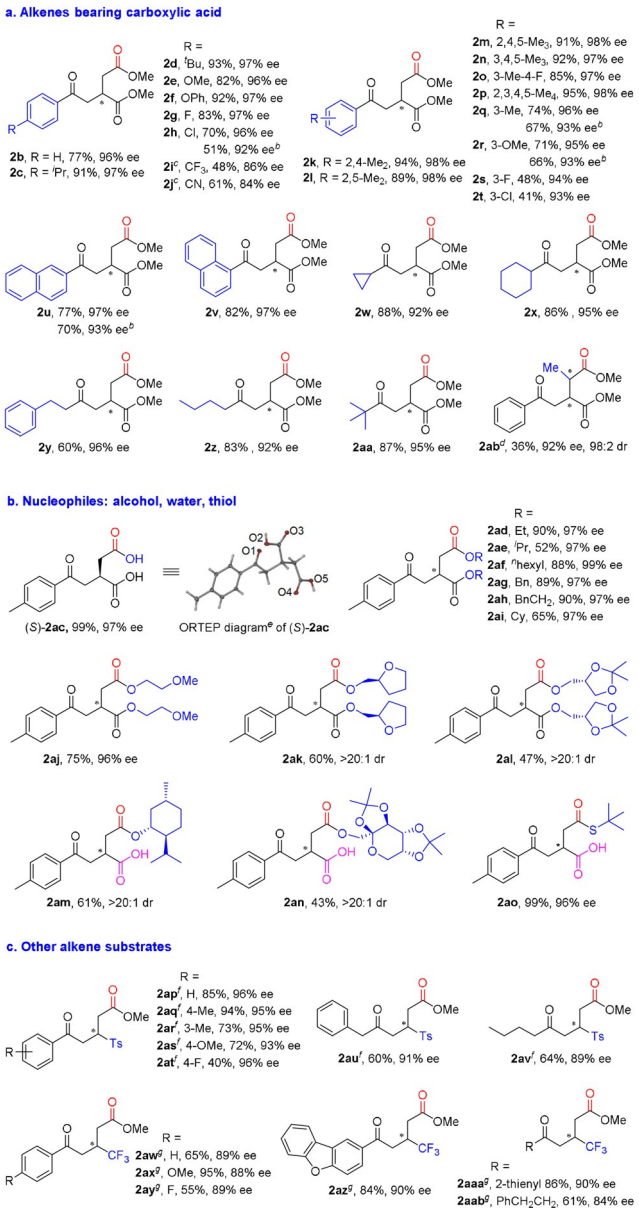
Tabelle 1: Asymmetric methoxycarbonylation of **1a**: Optimization of the reaction conditions.[a]



Entry	Solvent	L	*T* [°C]	*x*/*y*/*z*	Yield [%][b]	*ee* [%][c]
1	MeOH	**L1**	60	10/12/24	82	70 (+)
2	^{n}hexane	**L1**	60	10/12/24	86	79 (+)
3	toluene	**L1**	60	10/12/24	79	87 (+)
4	THF	**L1**	60	10/12/24	0	–/–
5	toluene	**L2**	60	10/12/24	99 (95[d])	95 (−)
6	toluene	**L3**	60	10/12/24	85	93 (−)
7	toluene	**L4**	60	10/12/24	65	10 (+)
8	toluene	**L5**	60	10/12/24	10	23 (+)
9	toluene	**L2**	60	2/2.4/24	99 (94[d])	95 (−)
10	toluene	**L2**	40	2/2.4/24	90 (84[d])	96 (−)
11	toluene	**L2**	40	2/2.4/48	99 (96[d])	96 (−)
12	toluene	**L2**	rt	2/2.4/48	72[d]	97 (−)
13[e]	toluene	**L2**	60	0.2/0.24/48	86[d]	94 (−)
14[f]	toluene	**L2**	60	10/12/24	87	86 (−)
15[f]	toluene	**L2**	40	2/2.4/48	89	93 (−)

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (0.2–10 mol%), ligand (0.24–12 mol%), PTSA·H_2O (24–48% mol%), CO (30 bar), MeOH (3 equiv), solvent (1 mL), rt-60 °C, 24 h. [b] Determined by GC analysis using *n*-decane as the internal standard. [c] Determined by chiral HPLC. [d] Isolated yield. [e] **1a** (4.0 mmol), toluene (5 mL), 48 h. [f] Replacing **1a** with the corresponding methyl ester. PTSA·H_2O = *p*-toluenesulfonic acid monohydrate.

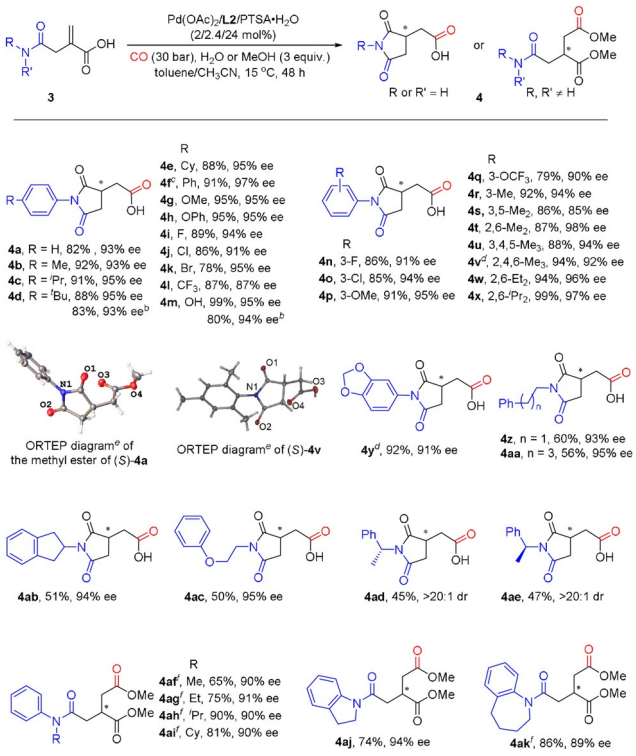
With the optimized conditions in hand, the compatibility and scope of alkenes **1** and nucleophiles were investigated in the asymmetric alkoxycarbonylation (Scheme 2). Various functional groups including both electron-donating (alkyl, methoxyl, and phenoxy) and electron-withdrawing (fluoro, chloro, trifluromethyl, and cyano) substitutes on the phenyl ring of the alkenes were well tolerated, affording the corresponding esters **2b**–**2t** with high enantioselectivities and moderate to excellent yields (84–98% *ee* and 41–95% yields, Scheme 2, a). Generally, higher yields were observed with electron-rich groups (**2c**–**2f** and **2k**–**2r**) than those with electron-deficient ones (**2g**–**2j** and **2s**–**2t**). No influence of the substitute at the *para*-, *meta*- or *ortho*-position on the phenyl ring was observed. Naphthyl-based substrates proved to be suitable, giving **2u** and **2v** with both 97% *ee* and good yields. Asymmetric hydrocarbonylation of substrates **1h**, **1q**, **1r**, and **1u** with the catalyst loading of 0.2 mol% attained the corresponding products in moderate to good yields and excellent enantioselectivities. The merit of broader substrate scope was further manifested by employing various aliphatic ketones featured with cyclic (**2w** and **2x**), acyclic (**2y** and **2z**) and ^{t}butyl alkyl (**2aa**) groups, giving the corresponding esters



Scheme 2. Asymmetric alkoxycarbonylation of β-ketone alkenes: Substrate scope.[a] [a] Reaction conditions: **1** (0.4 mmol), $Pd(OAc)_2$ (2 mol%), **L2** (2.4 mol%), PTSA·H_2O (48 mol%), CO (30 bar), NuH (3 equiv), toluene (1 mL), 40°C, 24 h. Isolated yields. ee values were determined by chiral HPLC. dr values were determined by ^{1}H NMR analysis. [b] **1** (2.0 mmol), $Pd(OAc)_2$ (0.2 mol%), **L2** (0.24 mol%), PTSA·H_2O (48 mol%), CO (30 bar), MeOH (3 equiv), toluene (4 mL), 60°C, 48 h. [c] $Pd(OAc)_2$ (5 mol%), **L2** (6 mol%), 60°C, 48 h. [d] **1ab** (0.2 mmol),$Pd(OAc)_2$ (10 mol%), (*S*)-SEGPHOS (12 mol%), PTSA·H_2O (48 mol%), 40°C, 24 h. [e] Thermal ellipsoids set at 50% probability. [f] **1** (0.2 mmol), $Pd(acac)_2$ (10 mol%), (*R*)-SEGPHOS (12 mol%), PTSA·H_2O (25 mol%), toluene (2 mL), 60°C. [g] **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), (*R*)-DM-SEGPHOS (6 mol%), PTSA·H_2O (48 mol%), MeOH (1 mL), 60°C. Ts = *p*-toluenesulfonyl.

with the same level of enantioselectivity and activity. Interestingly, tri-substituted alkenes also underwent the carbonylation well under modified reaction conditions leading **2ab** in acceptable yield with excellent enantioselectivity and diastereoselectivity. For the asymmetric carbonylation of **1a**, more than alcohol and water, *tert*-butyl thiol was also suitable nucleophile, proving the versatility of this method (Scheme 2, b). Specially, the hydroxycarbonylation of **1a** with 3 equiv of H_2O proceeded well, and the acid **2ac** was obtained in quantitative yield with 97% *ee*. The absolute configuration of **2ac** was confirmed to be (*S*) by X-ray diffraction analysis.[13] Other oxygen nucleophiles, such as primary (**2ad** and **2ah**), secondary (**2ae**), benzyl (**2ag**), and cyclohexyl alcohol (**2ai**) as well as ethylene glycol monomethylether (**2aj**), underwent the transformation smoothly in acceptable to high yields with excellent enantioselectivity. Last but not the least, some biomass-based and natural alcohols also showed good reactivity and diastereoselectivity as well. For instance, nucleophiles derived from furfural (**2ak**), glycerol (**2al**), and fructose (**2an**) as well as menthol (**2am**) can be used in this approach and synthetically useful yields with diastereoselective ratio of >20/1 were obtained. It is noteworthy that by tuning the type of the alcohol, the mono-ester products **2am** and **2an** can be selectively obtained, respectively. Compared to oxygen nucleophile, the thiocarbonylation of alkenes employing thiol as the nucleophile is more challenging due to its strong binding affinity to late-transition metals that could cause loss of catalyst activity.[14] Such asymmetric carbonylation could proceed with tert-butyl thiol as the nucleophile and mono-thioester **2ao** was afforded in quantitative yield with 96% *ee*. When using secondary/primary thiols including 1-pentanethiol and cyclohexanethiol as the nucleophiles for the asymmetric carbonylation, no desired carbonylation occurred. The asymmetric methoxycarbonylation of other functionalized alkenes, in which the -CO_2H substituent was replaced by sulfonyl (-Ts) and trifluoromethyl (-CF_3) groups, was also investigated (Scheme 2, c). After slightly modifying the reaction conditions, the substrates were transformed well into the corresponding products **2ap**–**2av** and **2aw**–**2aab** in moderate to excellent yields with high enantioselectivities. In these examples, the ketone moiety with (hetero)aryl or alkyl substituent was well tolerated. The expansion of olefinic substituents from -CO_2H/-CO_2Me to -Ts and -CF_3 groups further validated the design principle of using the carbonyl functionality to determine the enantioselectivity.

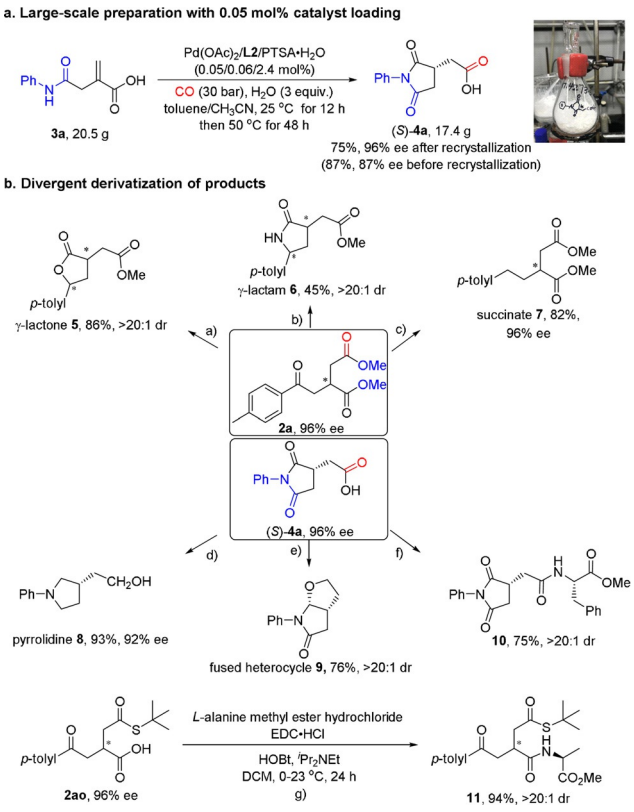
Encouraged by these results, we turned our attention to exploring carboxylic amide as the DG for asymmetric hydrocarbonylation. After optimizing the reaction conditions using α-methylene-γ-amide carboxylic acid **3a** as the substrate, the reaction was performed with H_2O as the nucleophile under 30 bar CO in a mixed solvent of toluene/CH_3CN (1/1 v/v) at 15°C for 48 h. To our delight, the desired cyclic imide **4a** was attained in 82% yield and 93% *ee* (Scheme 3). Further investigating the substrate scope and compatibility revealed that neither the electron properties nor the position of the substitution on the phenyl ring of **3** had impact on the reaction performance, providing the target products **4b**–**4y** in high yields with excellent enantioselectivities (85–98% *ee* and 78–99% yields). Various functional groups, including alkoxy, halide, trifluromethoxy, hydroxy, and methylenedioxy, were well tolerated in the reaction systems. The catalyst loading can be reduced to 0.2 mol% for substrates **3d** and **3m**, and the same level of activity and enantioselectivity were kept.



Scheme 3. Asymmetric hydroxyl- and methoxycarbonylation of β-amide alkenes: Substrate scope.[a] [a] Reaction conditions: **3** (0.4 mmol), $Pd(OAc)_2$ (2 mol%), **L2** (2.4 mmol%), PTSA·H_2O (24 mol%), CO (30 bar), H_2O or MeOH (3 equiv), toluene/CH_3CN (0.5/0.5 mL), 15 °C, 48 h. Isolated yields. ee values were determined by chiral HPLC. dr values were determined by ^1H NMR analysis. [b] **3** (2 mmol), $Pd(OAc)_2$ (0.2 mol%), **L2** (0.24 mol%), PTSA·H_2O (24 mol%), CO (30 bar), H_2O (3 equiv), toluene/MeCN (2.0/2.0 mL), 30 °C, 60 h. [c] 40 °C. [d] 30 °C. [e] Thermal ellipsoids set at 50% probability. [f] **3** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), **L2** (6 mol%).

The absolute configurations of **4v** and the methyl ester of **4a** were both confirmed to be (*S*) by X-ray diffraction analysis.[13] A series of cyclic and acyclic aliphatic amides were carbonylated enantioselectively with moderate activity (**4z**–**4ae**). The diastereomeric ratios of products **4ad** and **4ae** demonstrated the stereogenic center on the amide moiety had no impact on the enantioselective control of this asymmetric hydrocarboxylation. When *N*,*N*-disubstituted amides were employed as the substrates with MeOH as the nucleophile, the carbonylation products **4af**–**4ak** were obtained in good yields and high *ee* values.

To examine the efficiency and practicability of this approach, multi-gram scale synthesis was carried out for the asymmetric methoxycarbonylation of **3a**. Remarkably, the palladium catalyst loading could be reduced to 0.05 mol%, which represents the state-of-the-art activity among the reported enantioselective alkoxycarbonylation. By removing the catalyst through filtration and the solvent under reduced pressure, the crude product was obtained in 87% yield with 87% *ee* value. Recrystallization of the solid gave 17.4 g of cyclic imide **4a** in 75% yield and 96% *ee* indicating the presence of enantiomeric enrichment (Scheme 4, a). Then, the synthetic utility of our approach was demonstrated by divergent derivatization of the carbonylation products

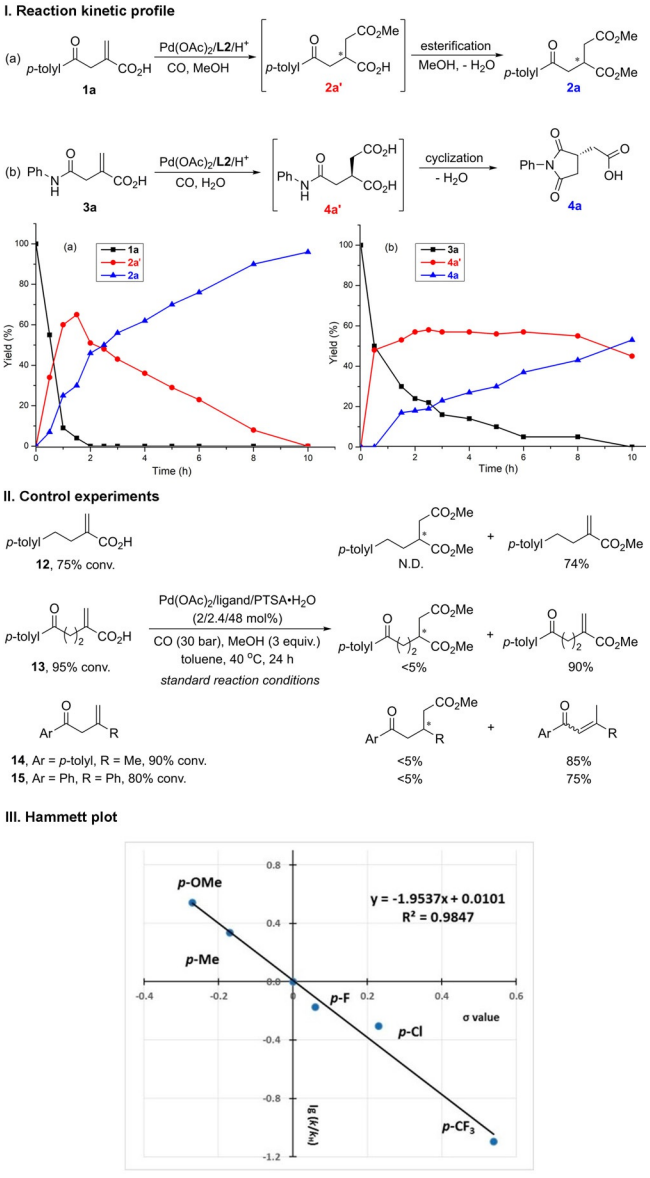


Scheme 4. Large-scale reaction and divergent derivatization of the products. Reaction conditions: [a] **2a** (0.2 mmol), $NaBH_4$ (0.24 mmol), MeOH (1 mL), 0 °C, 1.5 h. [b] 1) **2a** (0.2 mmol), NH_2OH·HCl (0.3 mmol), NaOAc (0.5 mmol), MeOH (2 mL), reflux, 8 h; 2) Raney Ni (>90%, 100 mg), H_2 (30 bar), MeOH (2 mL), rt, 24 h. [c] **2a** (1 mmol), Pd/C (10%, 50 mg), H_2 (40 bar), MeOH (5 mL), rt, 24 h. [d] **4a** (0.2 mmol), $LiAlH_4$ (4.0 mmol), THF (4 mL), reflux, 22 h. [e] **4a** (0.4 mmol), $NaBH_4$ (0.96 mmol), I_2 (0.4 mmol in 2 mL THF), THF (4 mL), 0 °C to reflux, 18 h. [f] **4a** (0.2 mmol), *L*-phenylalanine methyl ester hydrochloride (0.22 mmol), 1-ethyl-3-(3-dimethyllaminopropyl)-carbodiimide hydrochloride (EDC·HCl, 0.24 mmol), 1-hdroxybenzotriazole (HOBt, 0.24 mmol), $^iPr_2NEt$ (0.5 mmol), CH_2Cl_2 (2 mL), 0–23 °C. [g] **2an** (0.2 mmol), *L*-alanine methyl ester hydrochloride (0.22 mmol), EDC·HCl (0.24 mmol), HOBt (0.24 mmol), $^iPr_2NEt$ (0.5 mmol), CH_2Cl_2 (2 mL), 0–23 °C, 24 h.

(Scheme 4, b). For examples, biologically active γ-lactone **5** and γ-lactam **6** were prepared conveniently with one-pot manner in moderate to high yields and excellent diastereoselectivities from **2a** by simple reduction-related processes. The oxygen atom of the ketone group can be readily dismantled by hydrogenation with palladium-on-charcoal catalyst, giving the succinate **7** in 82% yield and 96% *ee*. Chiral cyclic imide **4a** could be readily converted into optically active pyrrolidine **8** and fused heterocycle **9** in high yields and stereoselectivity. Condensation of **4a** and **2ao** with α-amino acids (*L*-phenylalanine methyl ester, *L*-alanine methyl ester) afforded chiral amides **10** and **11** in high yields and diastereoselectivities. The diversity of these transformations exemplified the potential utility of our reaction system in organic synthesis by simple FGI.

To probe the mechanism for this highly efficient asymmetric alkoxy- and hydroxy-carbonylation, kinetic profile was

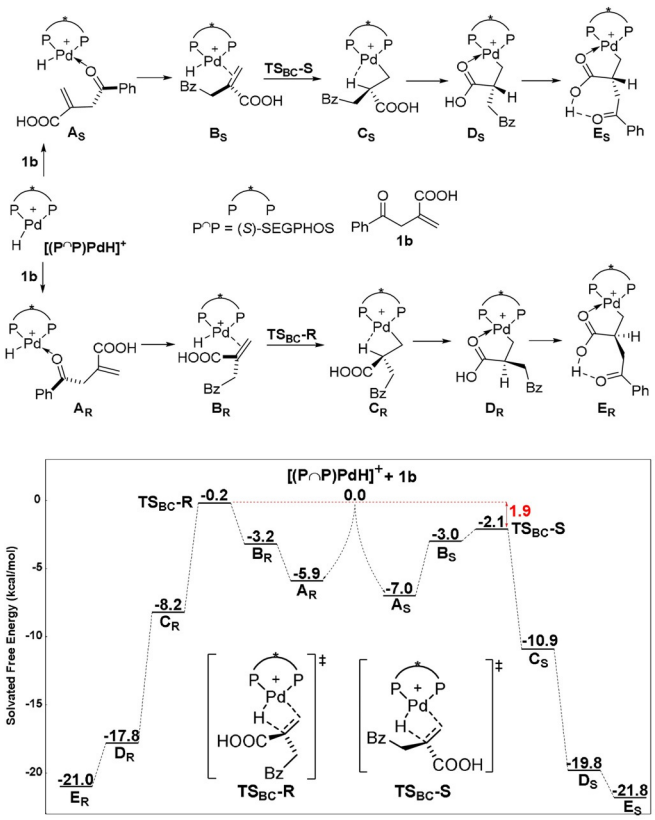
depicted and a set of control experiments on the effect of the ketone group was performed (Scheme 5). By monitoring the compound distribution for the carbonylation of **1a** and **3a** with ex-situ NMR, the kinetic progress of these two-step processes was plotted (Scheme 5, I). The substrate **1a** was quantitatively converted into the carbonylation mono-ester **2a′** within 2 hours, which was then esterified with alcohol to give the ester product **2a** at a relatively lower rate. During the reaction course, **2a** accumulated steadily and no direct esterification between **1a** and MeOH was observed. This pattern implied that **2a** was formed through methoxycarbonylation followed by acid-catalyzed esterification with MeOH, and the rate of hydrocarbonylation was faster than that of subsequent esterification. Similar reaction profile was disclosed for the hydroxycarbonylation of **3a**, that is, **3a** was initially converted to the acid **4a′**, then the following cyclization of this compound occurred to give the cyclic imide **4a**. The cyclization of **4a′** is relatively sluggish than the hydrocarbonylation. To get more insights in the role of the functionalized substituents, a set of the analogues of **1a**, such as **12** without β-ketone group, **13** with longer carbon chain, **14**/**15** using methyl/phenyl substituent instead of carboxylic acid group, was prepared and subjected to the standard reaction conditions (Scheme 5, II). After replacing **1a** by **12**, the reactivity of desired hydrocarbonylation decreased significantly and the direct esterification product was obtained in 74% yield. Acrylic acid **13** failed to undergo the hydrocarbonylation, and the esterification product was detected in 90% yield. When the carboxylic acid group in **1a** was replaced by methyl or phenyl group, the isomerization of terminal alkene **14**/**15** turned to be dominated, and less than 5% carbonylation product was detected. These control results unambiguously revealed the critical role of the carbonyl group in controlling the enantioselectivity as well as favoring the activity for asymmetric hydrocarbonylation, and the presence of electron-withdraw functional groups could inhibit proton acid-catalyzed alkene isomerization probably by destabilizing the tertiary carbocation intermediates. The observed distinct reactivity difference among the substrates listed in Scheme 2 led us to survey the electronic effect of substituents at the *para* position of the phenyl ring in β-ketone alkene (**1a**, **1e**, **1g**, **1h** and **1i**) on the rate of methoxycarbonylation in detail. According to the Hammett equation, the relative rates of the reaction compared to the unsubstituted compound (k/k_H) are plotted against the substituent constant (σ), yielding ρ value (−1.95, $R^2 = 0.98$, Scheme 5, III). The negative ρ value indicates the development of positive charge at the reaction center in the transition state of the rate-limiting step, which means the reaction rate is suppressed by electron-withdrawing substituents.



Scheme 5. Mechanistic studies. I. Reaction kinetic profile. II. Control experiments. III. Hammett plot.

To provide further insights into the origin of enantioselectivity and the role of β-carbonyl moiety in this asymmetric hydrocarbonylation process, density function theory computation was carried out by using the local meta-generalized gradient approximation M06L functional,[15] which includes dispersion correction. To save the computational cost, the combination of Karlsruhe basis sets[16] with Weigend06 density fitting auxiliary basis set[17] was utilized. In previous reports on mechanistic studies of alkene alkoxycarbonylation, pathway initiating from palladium hydride is generally accepted, wherein a cationic palladium hydride phosphine complex is frequently proposed as the active species of palladium-catalyzed hydrocarbonylation.[18] Herein this reaction was assumed to follow this mechanism, and we also treated the cationic palladium hydride complex as the active catalyst. Given the similar enantioselectivity produced by (*S*)-SEGPHOS and (*S*)-DIFLUORPHOS, the former ligand was employed in our computational model and the substrate **1b** was selected as the model olefin. The computed free-energy changes included the implicit solvation effect of toluene by SMD model.[19]

The results of DFT computation identified that the molecule without ketone- or enol-form intramolecular hydrogen bond is the major state of free **1b** in the toluene solution (detailed results see Figure S6 in SI). Regarding the coordination of **1b** with [((*S*)-SEGPHOS)PdH]$^+$ (denoted as



Scheme 6. The solvated free-energy changes of alkene insertion into Pd-H to generate a chiral center with different configuration.

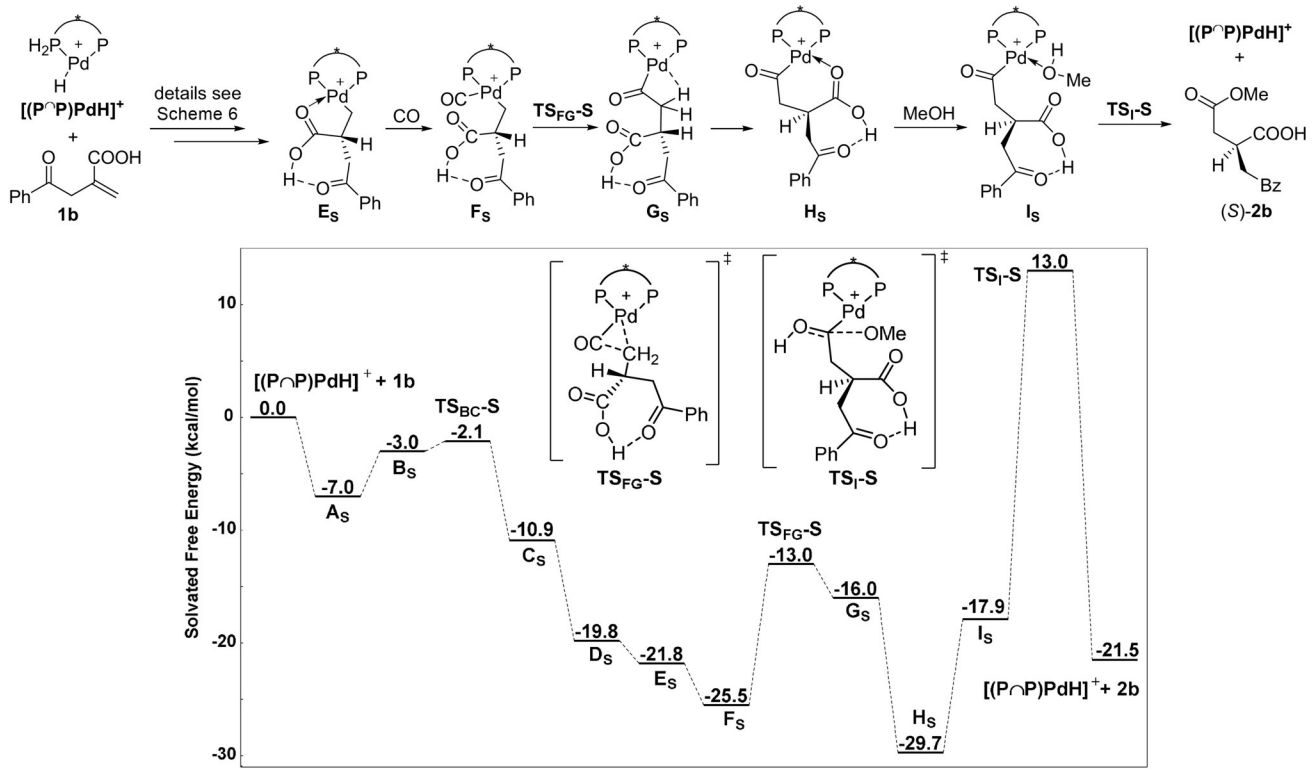
[(P∩P)PdH]$^+$ in Scheme 6), the ketone-coordinated cationic palladium hydride complexes $\mathbf{A_s}$ were relatively more stable than the corresponding alkene-coordinated complexes $\mathbf{B_s}$ by 4.0 kcal mol^{-1} (detailed results see Figure S7 in SI). Thus, the coordination of unsaturated cationic palladium hydride complex with the ketone site of **1b** has priority over the direct coordination with alkene group, and is regarded as the starting point of pathway towards hydrocarbonylation product. Such coordination between the ketone group and Pd^{II} fixes the prochiral face of alkene group towards the Pd^{II}-H moiety of active species **[(P∩P)Pd^{II}H]**$^+$. We found that complex $\mathbf{A_S}$ with the *Si*-face of prochiral C=C bond exposed to the Pd^{II} center is more thermodynamically favored by 1.1 kcal mol^{-1} than the diastereomeric complex $\mathbf{A_R}$ with the *Re*-face of C=C bond exposed to the metal center (ball-and-stick structures of $\mathbf{A_S}$, $\mathbf{B_S}$ and $\mathbf{TS_{BC}}$**-S** as well as $\mathbf{A_R}$, $\mathbf{B_R}$ and $\mathbf{TS_{BC}}$**-R** see section 7.4 in SI). Through intramolecular ligand exchange, the intermediates **A** were transformed to the corresponding alkene-coordinated intermediates **B**. During this process, the molecular conformation of **1b** remained unchanged. Subsequent insertion of the coordinated C=C bond into Pd-H afforded Pd-alkyl intermediate **C** bearing intramolecular Pd···H-C agostic interaction ($\mathbf{TS_{BC}}$). Owing to the presence of carboxylic acid group, the Pd-alkyl complexes **C** could be further converted to the more stable carbonyl-coordinated Pd-alkyl complexes **D**.

On the basis of the process, the ketone group plays the role of anchoring the spatial orientation of substrate **1b** by the coordination of oxygen atom with the (*S*)-SEGPHOS-chelated Pd^{II} center. According to the proposed mechanism, the enantioselectivity is determined by the insertion of the C=C bond of the olefin into Pd-H to form alkyl complexes (**B**→**C** via $\mathbf{TS_{BC}}$). For this crucial elementary step, significant difference on the energy barrier between the channels towards (*R*)- and (*S*)-products is found. The energy barrier for Pd-H insertion on the route towards (*S*)-configuration is only 0.9 kcal mol^{-1}, while that towards the (*R*)-configuration is as high as 3.0 kcal mol^{-1}. The free energy of $\mathbf{TS_{BC}}$**-R** was 1.9 kcal mol^{-1} higher than that of $\mathbf{TS_{BC}}$**-S** (Scheme 6), indicating generation of the (*S*)-configuration is indeed more kinetically favorable. Derived from this energy difference with Eyring equation, the theoretical *ee* value of product **2b** is 92 %, which is reasonably in line with the enantioselectivity of experimental data (**2b**, 96 % *ee*) shown in Scheme 2. Thus this computational model well explained the experimentally observed high enantioselectivity assisted by the β-carbonyl group of **1b**.

To gain a full understanding of the reaction mechanism, the overall free-energy changes for the transformation from substrate **1b** to product (*S*)-**2b** are depicted by DFT-based calculation (Scheme 7). After the insertion of alkene into the Pd–H bond, the generated intermediate $\mathbf{D_S}$ is transformed to the more thermodynamically stable intermediates $\mathbf{E_S}$ by establishing intramolecular seven-membered hydrogen-bond interaction between the carboxylic acid and ketone carbonyl groups. Comparing with the scenario without this intramolecular hydrogen-bond interaction, the presence of such interaction reduces the free energy of transition state for the endothermic migratory CO insertion ($\mathbf{F_S}$→$\mathbf{G_S}$ via $\mathbf{TS_{FG}}$**-S**) by 2.2 kcal mol^{-1} (see Figure S8 in SI). Transforming the intramolecular agostic Pd···H-C interaction to the coordination of carboxylic group with Pd center gives more stable species $\mathbf{H_s}$. In the final methanolysis, the external MeOH coordinates with Pd center instead of the carboxylic group affords the intermediate $\mathbf{I_S}$. This step is endothermic by 11.8 kcal mol^{-1}. Afterwards, the proton and methoxide of MeOH are, respectively transferred onto the oxygen and carbon centers of carbonyl group, respectively in the concerted mode via the transition state of $\mathbf{TS_I}$**-S** to afford the chiral product **2b** and regenerate **[(P∩P)PdH]**$^+$. This step needs to surmount the energy barrier of 30.9 kcal mol^{-1} and thus becomes the rate-determining step of the overall process. In the transition state of the rate-determining step, the proton of hydroxy group in methanol was transferred onto the oxygen center of carbonyl group in acyl-palladium species, and a positive charge at the reaction site was built ($\mathbf{TS_I}$**-S**). The structure and energy pattern of $\mathbf{TS_I}$**-S** well explained the negative ρ value of the Hammett plot determined by experiments, which indicates the development of positive charge at the reaction center in the transition state of the rate-limiting step.

Conclusion

In conclusion, a highly efficient palladium-catalyzed asymmetric alkoxy- and hydroxyl-carbonylation of β-carbonyl functionalized alkenes with CO, and nucleophiles was



Scheme 7. The solvated free-energy changes for the process from substrate **1b** to the methoxycarbonylation product (*S*)-**2b** catalyzed by Pd/(*S*)-SEGPHOS.

developed, affording a range of chiral carboxylic acid derivatives with high enantioselectivity. The salient features of the protocol include broad substrate scope and mild reaction conditions. By virtue of the functional group interconversion of the carbonyl, the synthetic utility of the methodology was demonstrated in the ready transformation of the products into various biologically interesting chiral molecules, such as γ-lactone, γ-lactam, pyrrolydine, and amide. Control experiments and DFT calculation revealed that the β-carbonyl group is critical in controlling the enantioselectivity and enhancing the catalytic activity, while an electron-withdrawing vinyl substituent (e.g., -CO_2H, -CO_2Me, -Ts, -CF_3) was vital in inhibiting the alkene isomerization via carbocation. Further exploration on the asymmetric hydrocarbonylation with this approach is in progress in our lab and the results will be reported in due course.

Acknowledgements

National Nature Science Foundation of China is gratefully acknowledged for the general support. DFT calculations were performed at the Shanghai Supercomputing Centre.

Conflict of Interest

The authors declare no conflict of interest.

Stichwörter: asymmetric hydrocarbonylation · carbonyl groups · carboxylic acids · functionalized alkenes · palladium

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Manuskript erhalten: 3. Mai 2021
Akzeptierte Fassung online: 9. Juni 2021
Endgültige Fassung online: 2. Juli 2021

