Ligand-Enabled Reactivity and Selectivity in a Synthetically Versatile Aryl C H Olefination

Dong-Hui Wang, *et al.*

Science **327**, 315 (2010);
DOI: 10.1126/science.1182512

Both complexes $[2]^{4+}$ and $[3]^{4+}$ upon mixing with $LiClO_4$ in acetonitrile yield $[4]^{4+}$ as confirmed by ESI-MS spectrometry (Fig. 2 and figs. S27 and S28). Therefore, in another attempt to use the complex $[2]^{4+}$ as an electrocatalyst in this reaction, the electrochemical cell containing an acetonitrile solution of complex $[2]^{4+}$ and lithium perchlorate (as supporting electrolyte) was stirred to precipitate all the available oxalate. Then the solution was electrolyzed at –0.03 V versus NHE with continuous purging of CO_2. The consumption of current continued linearly for more than 3.3 hours, consuming three equivalents of charge (12 electrons) per four copper ions, with concurrent crystallization of lithium oxalate. Thereafter, the rate of the reaction gradually decreased as the crystallized lithium oxalate started to cover the electrode surface, thereby hampering electron transfer (fig. S29). In total, the electrocatalysis could be extended for more than 7 hours, with consumption of 6 equivalents of charge (24 electrons) and generating 12 equivalents of oxalate per molecule of $[2]^{4+}$.

We have thus devised an electrocatalytic system based on a copper coordination compound that is able to activate and convert CO_2 selectively into oxalate at readily accessible potentials, in the simple but very effective catalytic cycle shown in Fig. 3. The finding that a copper(I) system is oxidized by CO_2 rather than O_2 implies that the selective binding of CO_2 to the copper(I) ions offers a low-energy pathway for the formation of the $CO_2^{\bullet-}$ radical anion. The copper(II) oxalate complex $[2]^{4+}$ is thermodynamically favored; the binding of CO_2 to the Cu(I) centers in $[1]^{2+}$ and the formation of oxalate appears to be highly selective and relatively rapid. Because of the low solubility of lithium oxalate in acetonitrile, the release of the oxalate dianion from $[2]^{4+}$ in the presence of lithium perchlorate is instantaneous, generating the complex $[4]^{4+}$. Therefore, for the current system the electrocatalytic reduction of the copper(II) ion to copper(I) appears to be rate-limiting. The precipitation of the lithium oxalate formed during the reaction onto the electrode surface hampers efficient electron transfer. Tuning the redox potential of the copper complex by altering the ligand structure with a variety of substituents, immobilization of the complex onto the electrode surface, and improved methods for the removal of oxalate may result in improved efficiency of the catalytic system. We believe that our studies will instigate further development of coordination complexes for catalytic CO_2 sequestration, its selective conversion and use as fuels such as methanol or as feedstock in the synthesis of useful organic compounds.

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26. This work was supported by the Leiden Institute of Chemistry. X-ray crystallographic work was supported (M.L. and A.L.S.) by the Council for the Chemical Sciences of The Netherlands Organization for Scientific Research (CW-NWO). J. Reedijk and M. T. M. Koper are gratefully acknowledged for stimulating discussions. P.B. (Ithaca College, New York) was involved in the project through a summer exchange program. Crystallographic data for $[2](BF_4)_4$ and $[3](BF_4)_4$ have been deposited with the Cambridge Crystallographic Data Center under reference numbers 717726 and 717727.

Supporting Online Material

www.sciencemag.org/cgi/content/full/327/5963/313/DC1
Materials and Methods
SOM Text
Figs. S1 to S30
Tables S1 and S2
References

19 June 2009; accepted 25 November 2009
10.1126/science.1177981

Ligand-Enabled Reactivity and Selectivity in a Synthetically Versatile Aryl C–H Olefination

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The Mizoroki-Heck reaction, which couples aryl halides with olefins, has been widely used to stitch together the carbogenic cores of numerous complex organic molecules. Given that the position-selective introduction of a halide onto an arene is not always straightforward, direct olefination of aryl carbon-hydrogen (C–H) bonds would obviate the inefficiencies associated with generating halide precursors or their equivalents. However, methods for carrying out such a reaction have suffered from narrow substrate scope and low positional selectivity. We report an operationally simple, atom-economical, carboxylate-directed Pd(II)-catalyzed C–H olefination reaction with phenylacetic acid and 3-phenylpropionic acid substrates, using oxygen at atmospheric pressure as the oxidant. The positional selectivity can be tuned by introducing amino acid derivatives as ligands. We demonstrate the versatility of the method through direct elaboration of commercial drug scaffolds and efficient syntheses of 2-tetralone and naphthoic acid natural product cores.

Unactivated carbon–hydrogen (C–H) bonds are among the simplest and most common structural motifs in naturally occurring organic molecules, and, as such, they are ideal targets for chemical transformations. Although C–H bonds are generally unreactive, during the past several decades transition metal catalysis has emerged as an effective means of converting unactivated C–H bonds into carbon–heteroatom and carbon–carbon (C–C) bonds (*1*–*5*). This technology has proven to be valuable in natural products synthesis, where several distinct C–H functionalization strategies have been exploited (*6*–*12*).

Traditionally, C–C bonds between aryl and olefinic fragments have been forged through the Pd-catalyzed Mizoroki-Heck reaction, which couples aryl halides or triflates with olefins (Fig. 1A). Considering the prominence of this transformation in organic synthesis (*13*), Pd-catalyzed olefination of aryl C–H bonds has the potential to emerge as a powerful platform for more direct access to carbogenic cores of complex molecules (Fig. 1, A and E), particularly in cases in which the position-selective introduction of a halide is problematic. However, the few pioneering examples of Pd-catalyzed C–H olefination in total synthesis to date are restricted to specific cases, generally including electron-rich heterocycles, such as indoles and pyrroles, and/or

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stoichiometric palladium (*14*–*17*). The development of Pd-catalyzed arene C–H olefination reactions to provide general routes to commonly occurring carbogenic motifs thus remains an outstanding challenge. This limitation is rooted in two interrelated problems. First, the substrates that are typically effective in palladium-catalyzed C–H activation are synthetically restrictive, either because they are limited to electron-rich arenes or heterocycles, or because they possess impractical chelating functional groups to promote metalation. These directing groups include those that are irremovable and recalcitrant to undergo further synthetic elaboration, such as pyridine, and those that are removable but require several steps for installation and detachment, such as oxazoline (*5*). Second, methods for effecting position-selective C–H activation on multiply substituted arenes (*18*, *19*), particularly via ligand control, remain underdeveloped.

Here, we report a catalytic system that addresses these problems. A practical Pd-catalyzed reaction using molecular oxygen as the terminal oxidant has been developed to perform C–H olefination with synthetically useful phenylacetic acid and 3-phenylpropionic acid substrates. This reaction has remarkably broad substrate scope, which is enabled in part by the use of amino acid ligands to enhance the reactivity of the catalytically active Pd(II) species. Moreover, two distinct methods to control the positional selectivity of C–H activation with multiply substituted arenes have been demonstrated: (i) substrate control, by appending a protecting group (PG) to modulate the intrinsic steric bias; and (ii) catalyst control, by using ligands to alter the steric and electronic properties around the metal center (Fig. 1B). The versatility of this olefination reaction is demonstrated by direct functionalization of commercially available drugs (Fig. 1D) and by atom- and step-economic syntheses of 2-tetralone derivatives (**2**) (key synthetic intermediates for tetraline-based natural products) and two challenging naphthoic acid components in neocarzinostatin (**1**) and kedarcidin (**3**), highly active antibiotics (Fig. 1E).

As part of the overarching goal of developing practically useful C–H functionalization reactions, our laboratory has focused on discovering reactivity with broadly useful substrates, in which all moieties present in the starting material can be used for subsequent synthetic applications in an atom-economical manner. Following this philosophy, we sought to develop a Pd-catalyzed olefination protocol (*20*) for phenylacetic acid substrates, as the resulting carbon skeletons are well-established platforms for the synthesis of 2-tetralones and naphthoic acids. Although carboxy-directed C–H activation involving six atoms in the coordination assembly is rare, we hypothesized that our K^+-promoted Pd insertion procedure for benzoic and phenylacetic acids (*21*, *22*), which promotes C–H activation through the complex-induced proximity effect (*23*), could be exploited for subsequent olefination.

To this end, we began by extensively screening reaction conditions and optimizing with respect to solvent, inorganic base, temperature, and oxidant (see supporting online material). Gratifyingly, we found that 4-methoxyphenylacetic acid could be coupled with ethyl acrylate in the presence of 5 mol% $Pd(OAc)_2$ (Ac, acetyl) to give the desired product in high yield (Fig. 2, **6a$_1$**). As a further practical advantage, 1 atm of O_2 could be used as the terminal oxidant, with 5 mol% benzoquinone (BQ) serving as a ligand to prevent minor formation of the meta- and di-ortho-olefinated products.

A wide range of phenylacetic acid substrates were found to be compatible with this protocol (Fig. 2). Products containing chlorides (**6g**, **6h**, **6j**, **6k**, and **6p**), fluorides (**6f** and **6r**), and ketones (**6l**) could be obtained in high yields. Notably, the tolerance for chlorides on the aromatic ring in this ortho-olefination offers an opportunity for subsequent cross-coupling, facilitating expedient synthesis of highly complex biaryl molecules. Several drug substrates, including ketoprofen (**4l**), ibuprofen (**4n**), and naproxen (**4o**), were found to be compatible with this protocol, affording the respective olefinated products **6l**, **6n**, and **6o**. These results demonstrate the potential for applying C–H olefination to effect direct functionalization of existing bioactive molecular scaffolds in the interest of enabling drug diversification for medicinal chemistry.

A diverse array of substitution patterns at the α position were tolerated, with a higher degree of α substitution corresponding to higher activity resulting from the Thorpe-Ingold effect (**6j** to **6s**). Optically pure compounds with chiral centers at the α position were found to racemize slightly under our reaction conditions; for example, **6o** was formed in 72% enantiomeric excess (ee). In this case, the use of Li_2CO_3 as the base prevented racemization, affording the product in 97% ee, but also lowered the conversion to 24%.

A variety of different olefin coupling partners were found to react well using this catalytic sys-

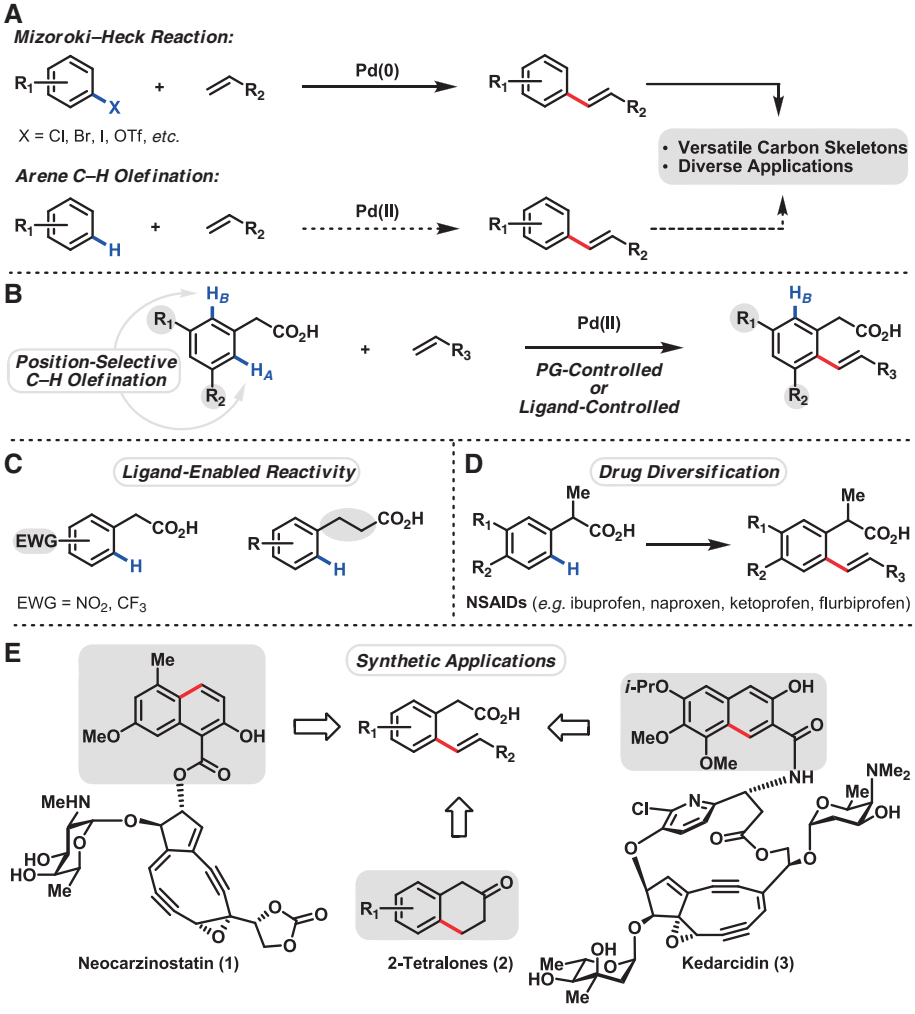


Fig. 1. (**A**) Comparison of the Mizoroki-Heck reaction and arene C–H olefination. (**B**) Schematic depiction of our position-selective C–H activation approach. (**C**) Substrates that were found to be unreactive under our original conditions but could be efficiently olefinated in the presence of amino acid ligands. (**D**) Direct ortho-olefination of commercial nonsteroidal anti-inflammatory drugs (NSAIDs). (**E**) Expedient synthesis of natural product components using position-selective C–H olefination.

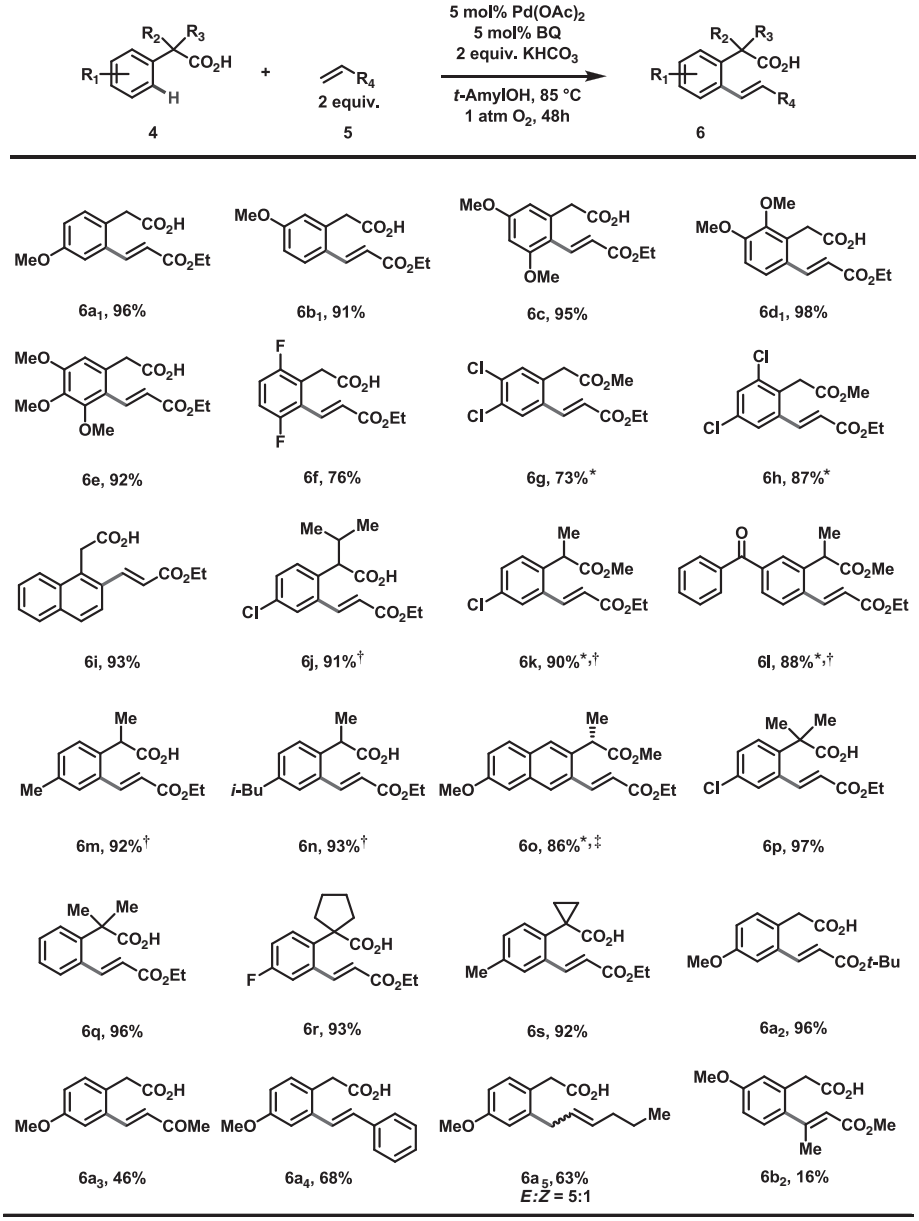
tem (Fig. 2, **6a$_2$** to **6a$_5$** and **6b$_2$**). Interestingly, using 1-hexene as the olefin, we found that nonconjugated product **6a$_5$** was formed predominantly (with a 5:1 ratio of *E*:*Z* alkene stereoisomers) over the thermodynamically favorable conjugated system (observed in only trace amounts). Mechanistically, this suggests that after 1,2 migratory insertion of the Pd–aryl moiety into the olefin, the resulting intermediate is conformationally restricted from undergoing subsequent β-hydride elimination with the benzylic hydrogen atoms. A possible explanation is that the carbonyl oxygen atom from the carboxylate group remains coordinated to palladium in an unusual eight-membered ring, which restricts the bond rotation necessary to align the metal for syn elimination. Synthetically, olefinated products such as **6a$_5$** represent a class of substrates beyond the scope of traditional Mizoroki-Heck–type chemistry.

With this highly efficient catalytic C–H olefination protocol in hand, we next sought to control the positional selectivity of this reaction with multiply substituted arenes that yielded isomeric product mixtures under our original conditions (Fig. 1B). For instance, 3-methoxy-5-methylphenylacetic acid (**7**) reacted to form a mixture of positional isomers without substantial bias (1.4:1, **8-A**:**8-B**) (Fig. 3A, entry 1). We hypothesized that tuning the steric properties of the metal center through the coordination of a ligand could provide the site recognition that we sought. Extensive screening of ligands led us to discover that mono-N-protected amino acids were effective in this respect (*24*). During our screening efforts, we observed that the resulting isomeric distribution was substantially dependent on the structure of the amino acid side chain, with Boc-Leu-OH and Boc-Ile-OH giving the best selectivity (7:1 and 8:1, respectively; Boc, *tert*-butoxycarbonyl) (Fig. 3A, entries 5 and 6). We were pleased to find that positional selectivity could be further enhanced by varying the N-protecting group, with Formyl-Ile-OH as the best ligand, giving a 20:1 ratio of positional isomers (Fig. 3A, entry 12). The conversion using this particular ligand was slightly lower than without it, but by increasing the catalyst loading to 7%, the conversion could be improved to 75%. Allowing the reaction to run for 96 hours further improved the conversion to 89%.

This ligand-controlled, position-selective C–H olefination protocol could also be applied to other multiply substituted arene substrates, including natural product precursors such as **9** and drug substrates such as flurbiprofen (**11**) (Fig. 3B). With substrate **9**, because the two ortho-C–H bonds are approximately electronically equivalent, the outstanding positional selectivity observed with Boc-Ile-OH is likely a result of the catalyst's recognition of the different steric environments. In contrast, both steric and electronic properties could be contributing to the improvement in positional selectivity with substrates **7**, **11**, **13**, and **15**; the mechanistic details in these cases remain to be fully elucidated. (Unless otherwise noted, the reaction conditions in Fig. 3, B to D, are identical to those described in Fig. 3A.)

To our delight, during this investigation, we also discovered that certain Boc-protected amino acid ligands could markedly improve the yield in this olefination reaction (see supporting online material), with the optimal ligand choice highly dependent on the combination of substrate and coupling partner. For instance, using Boc-Ile-OH, olefinated products **6t** and **17** could be formed quantitatively, even when the catalyst loading was reduced to 1 to 2 mol% of $Pd(OAc)_2$ (Fig. 3C). Moreover, the use of amino acid ligands allowed for efficient di-olefination, fashioning product **17**, for example, in quantitative yield. Thus, our parent C–H olefination protocol and the amino acid–ligated system offer complementary reactivity to access either the mono- or di-olefinated products, depending on which is more useful for a given synthetic application (Fig. 2 and Fig. 3C, respectively).

The strong ligand influence on reactivity in this system encouraged us to examine whether previously unreactive 3-phenylpropionic acid and electron-deficient phenylacetic acid substrates could now be ortho-olefinated in the presence of amino acid ligands. Indeed, we were pleased to find that an array of such substrates



*The corresponding phenylacetic acid substrate was used as starting material; to simplify separation, the product was isolated as the methyl ester following treatment of the crude reaction mixture with CH_2N_2. †Racemic starting material was used. ‡Optically pure naproxen (**4o**, 97% ee) was used as the starting material. The product was obtained in 72% ee. The use of Li_2CO_3 as the base gave 24% conversion (by ^{1}H NMR) and 97% ee. The ee values were determined by chiral HPLC.

Fig. 2. C–H olefination of phenylacetic acid substrates with ethyl acrylate (**6a$_1$**, **6b$_1$**, and **6c** to **6s**) and with other olefin coupling partners (**6a$_2$** to **6a$_5$** and **6b$_2$**).

could be olefinated in moderate to good yields (Fig. 3D). Notably, the synthetic flexibility afforded by the extra methylene spacer in **18a** and **18b** greatly expands the range of core structures that can subsequently be accessed.

Finally, we demonstrated the synthetic utility of this highly versatile and scalable olefination reaction by concise syntheses of several natural product core structures, including 2-tetralones and naphthoic acids (Fig. 4). The synthesis of natural products of this type is by no means simple, but impressive efforts by several groups (*25*–*29*) have led to a basic roadmap for how to construct such molecules. In particular, olefinated arenes with structures analogous to **10-A** (Fig. 4C) often serve as key intermediates, and the olefinic moieties are usually introduced via a Wittig reaction with the corresponding aldehyde or via bromination in the early stages to set up a late-stage Mizoroki-Heck reaction. Our C–H olefination reaction offers a departure from these approaches both in the retrosynthetic sense (in that it represents a different synthetic disconnection associated with a distinct pool of starting materials) and in the forward sense (in that the key transformations are highly step- and atom-economical).

Using our original protocol (Fig. 2), commercially available 2,3-dimethoxyphenylacetic acid (**4d**) could be transformed to intermediate $\mathbf{6d_2}$ in high yield. A straightforward sequence of hydrogenation, ester formation, Dieckmann condensation, and decarboxylation yielded 2-tetralone derivative **19** (Fig. 4A) (*29*). Notably, nearly all substrates described in this work could potentially be used to synthesize a diverse range of 2-tetralones.

Next, we demonstrated the utility of both protecting group–controlled and ligand-controlled position-selective olefination by synthesizing the naphthoic acid components of both neocarzinostatin (**1**) and kedarcidin (**3**) (Fig. 4). The use of a triisopropylsilyl (TIPS) group afforded the desired positional selectivity for the preparation of **21-A** (Fig. 4B). This key intermediate could then be cyclized in accordance with literature precedent (*28*) to give the naphthoic acid component **22** of neocarzinostatin (**1**) (*26*). On the other hand, the ligand-controlled position-selective olefination of **9** afforded **10-A** in high yield (Fig. 4C). **10-A** could then be converted into the desired naphthoic acid product (**23**) following a two-step procedure developed by Myers and Hirama: formation of the acid chloride and [6π] electrocyclization (*25*, *27*). In all three of these cases, the reaction sequences are among the highest-yielding and most atom- and step-economical routes achieved to date for accessing these widely studied, commonly occurring core structures.

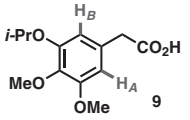
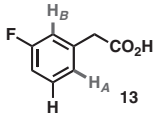
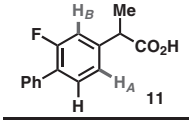
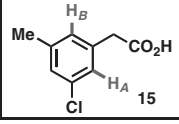
In this report we have attempted to demonstrate the importance of ligand development (*30*) for enabling unique reactivity and selectivity in C–H activation, as well as to illustrate two conceptual prerequisites for the widespread application of Pd-catalyzed C–H activation in organic synthesis: (i) versatile substrates and coupling partners, and (ii) precise control of positional selectivity in C–H functionalization. We anticipate that this C–H olefination reaction and others grounded in this philosophy will find broad applicability in multifarious synthetic endeavors.

A

Entry	Ligand	Conv. (%)*	A : B	Entry	Ligand	Conv. (%)*	A : B
1	---	68	1.4 : 1	7	Boc_2-Leu-OH	50	3 : 1
2	Boc-Tyr(Bzl)-OH	17	2.5 : 1	8	H-Leu-OH	16	6 : 1
3	Boc-Abu-OH	17	5 : 1	9	Formyl-Leu-OH	24	13 : 1
4	Boc-Val-OH	23	6 : 1	10	Fmoc-Ile-OH	16	5 : 1
5	Boc-Leu-OH	24	7 : 1	11	Ac-Ile-OH	23	10 : 1
6	Boc-Ile-OH	27†	8 : 1	12	Formyl-Ile-OH	43 (75)‡	20 : 1

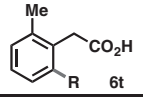
*Based on ^{1}H NMR. The di-olefinated product was formed in less than 5% conversion. †24 h. ‡7 mol% $Pd(OAc)_2$, 7 mol% BQ, 14 mol% L.

B

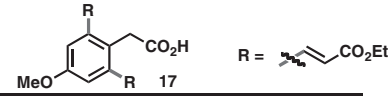
Substrate	Ligand	Conv. (%)*	A : B	Substrate	Ligand	Conv. (%)*	A : B
 9	---	65†	1.5 : 1	 13	---	63	1.6 : 1
	Boc-Ile-OH	86†	23 : 1		Formyl-Ile-OH	77	3.5 : 1
 11	---	82	2.8 : 1	 15	---	8	1.2 : 1
	Formyl-Ile-OH	78	5.7 : 1		Formyl-Ile-OH	50‡	4.7 : 1

*Based on ^{1}H NMR. Products derived from substrates **9**, **11**, **13**, and **15** are labeled **10-A/B**, **12-A/B**,**14-A/B**, and **16-A/B** respectively. Only the major products were isolated and characterized. †*t*-Butyl acrylate was used as the coupling partner. ‡15 mol% $Pd(OAc)_2$, 15 mol% BQ, 30 mol% Formyl-Ile-OH.

C


6t

$Pd(OAc)_2$	Ligand	Conv. (%)*,†
2 mol%	---	31
2 mol%	Boc-Ile-OH	>99

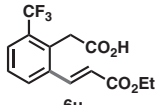
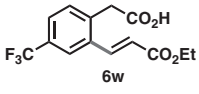
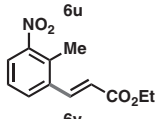
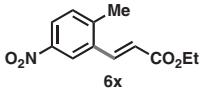
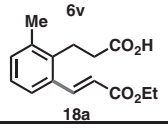
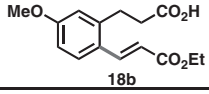


17

$Pd(OAc)_2$	Ligand	Conv. (%)*,†	Selectivity
2 mol%	---	10	mono
2 mol%	Boc-Ile-OH	>99	di

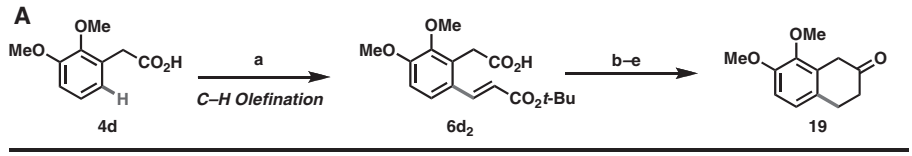
*Based on ^{1}H NMR. †2 mol% $Pd(OAc)_2$, 2 mol% BQ, 4 mol% Ligand.

D

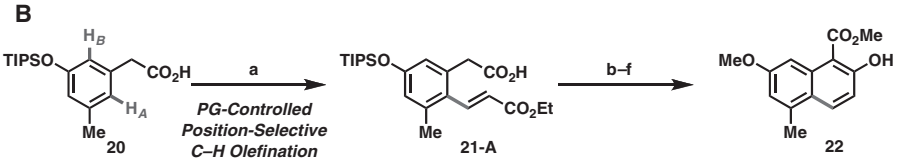
Product	Ligand	Yield (%)*	Product	Ligand	Yield (%)*
 6u	---	12	 6w	---	13
	Boc-Val-OH	90		Boc-Ile-OH	85‡
 6v	---	0	 6x	---	0
	Boc-Val-OH	50†		Boc-Val-OH	57§
 18a	---	8	 18b	---	22
	Boc-Val-OH	60		PG_1-Leu-OH‖	75¶

*Isolated Yield. †2-Nitrophenylacetic acid was used as substrate; the product was completely decarboxylated under the reaction conditions: 10 mol% $Pd(OAc)_2$, 10 mol% BQ, 20 mol% Boc-Val-OH. ‡Mono:Di = 2:1. §4-Nitrophenylacetic acid was used as substrate; decarboxylated:non-decarboxylated = 2:1. ‖PG_1 = (–)-Menthyl(O_2C). ¶Mono:Di = 3:1.

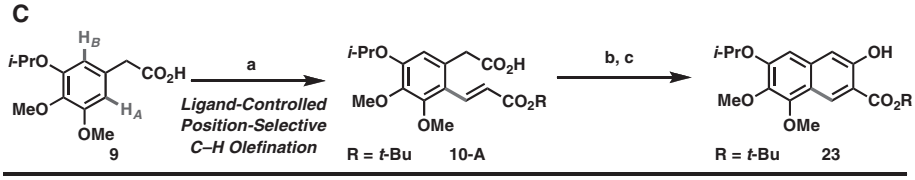
Fig. 3. (**A**) Selected amino acid ligand screening data for position-selective C–H olefination. (The full ligand screening data are available in table S8.) (**B**) Substrate scope for ligand-controlled position-selective C–H olefination. (**C**) Ligand-enabled C–H olefination with 2 mol% $Pd(OAc)_2$. (**D**) Amino acid ligand–enabled C–H olefination with problematic substrates.



Reagents and conditions: (a) $Pd(OAc)_2$, BQ, *t*-butyl acrylate, $KHCO_3$, *t*-AmylOH, O_2 (1 atm), 85 °C, 93%. (b) H_2 (balloon), Pd/C, MeOH, rt. (c) CH_2N_2, Et_2O, 0 °C, 93% (two steps). (d) KO*t*-Bu, Et_2O, rt. (e) HCl/HOAc, 110 °C, 69% (two steps).



Reagents and conditions: (a) $Pd(OAc)_2$, BQ, ethyl acrylate, $KHCO_3$, *t*-AmylOH, O_2 (1 atm), 85 °C, 77%, **A**:**B** = 10:1. (b) H_2 (balloon), Pd/C, MeOH, rt. (c) $Et_3N{\bullet}3HF$, THF, rt. (d) MeI, K_2CO_3, acetone, reflux, 69% (3 steps). (e) KO*t*-Bu, Et_2O, rt, 88%. (f) $BrCCl_3$, DBU, CH_2Cl_2, rt, 81%.



Reagents and conditions: (a) $Pd(OAc)_2$, BQ, *t*-butyl acrylate, $KHCO_3$, Boc-Ile-OH, *t*-AmylOH, O_2 (1 atm), 85 °C, 86%, **A**:**B** = 23:1 (without ligand, **A**:**B** = 1.5:1). (b) $(COCl)_2$, CH_2Cl_2, rt. (c) *i*-Pr_2NEt, CH_2Cl_2, rt, 87% (two steps).

Fig. 4. (**A**) Synthesis of 7,8-dimethoxytetalin-2-one. (**B**) Synthesis of the naphthoic acid component of neocarzinostatin (**1**). (**C**) Synthesis of the naphthoic acid component of kedarcidin (**3**).

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37. Supported by an A. P. Sloan Foundation fellowship (J.-Q.Y.); predoctoral fellowships from NSF, the U.S. Department of Defense, the Scripps Research Institute, and the Skaggs Oxford Scholarship program (K.M.E.); and the Scripps Research Institute, National Institute of General Medical Sciences grant 1 R01 GM084019-02, NSF grant CHE-0910014, Amgen, and Eli Lilly & Co.

Supporting Online Material

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Materials and Methods
Tables S1 to S8
NMR Spectra
References

28 September 2009; accepted 12 November 2009
Published online 26 November 2009;
10.1126/science.1182512
Include this information when citing this paper.

Nanoporous Gold Catalysts for Selective Gas-Phase Oxidative Coupling of Methanol at Low Temperature

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Gold (Au) is an interesting catalytic material because of its ability to catalyze reactions, such as partial oxidations, with high selectivities at low temperatures; but limitations arise from the low O_2 dissociation probability on Au. This problem can be overcome by using Au nanoparticles supported on suitable oxides which, however, are prone to sintering. Nanoporous Au, prepared by the dealloying of AuAg alloys, is a new catalyst with a stable structure that is active without any support. It catalyzes the selective oxidative coupling of methanol to methyl formate with selectivities above 97% and high turnover frequencies at temperatures below 80°C. Because the overall catalytic characteristics of nanoporous Au are in agreement with studies on Au single crystals, we deduced that the selective surface chemistry of Au is unaltered but that O_2 can be readily activated with this material. Residual silver is shown to regulate the availability of reactive oxygen.

An ever-increasing demand for resources enforces the need of sustainability in all arenas (*1*). This new challenge has triggered a growing interest in a "green chemical industry," especially for the production and processing of commodity chemicals (*2*, *3*), which is based on more efficient processes working under mild conditions (low temperatures and ambient conditions) and relying on cheap and abundant feedstock. In this context, gold (Au)–based catalysts have attracted considerable attention in the past decade because of their nontoxic nature and the ability to promote selective reactions at low temperatures. In particular, the potential of Au for partial oxidation reactions, such as the selective oxidation of alcohols (*4*–*6*) and hydrocarbons (*7*, *8*), was demonstrated in numerous studies. Model studies on single-crystal Au provided molecular-scale insight into the activity of gold, showing that atomic oxygen is the key species that promotes a range of selective oxida-

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