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Controlling Chemoselectivity in Vinyl and Allylic C−X Bond Activation with Palladium Catalysis: A pK_a-Based Electronic Switch

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Abstract: It has been demonstrated that the same Pd catalyst can be used to effect allylic substitution or vinylic cross-coupling reactions selectively and interchangeably on polyfunctionalized olefin building blocks despite the differences in reaction mechanism. This was achieved by altering the pK_a of the conjugate acid of the allylic leaving group while keeping the vinyl coupling partner constant. In the case of 2,3-dibromo-1-propene, Pd-catalyzed allylic ionization with malonate nucleophile proceeded selectively and quantitatively in the presence of the Suzuki reaction components necessary for cross-coupling. Conversely, the bromide of 2-bromo-1-(4-ethylphenoxy)-2-propene could be cross-coupled selectively without activation of the allylic phenoxy substituent. In both reactions, the same catalyst could then be used to complete the sequence, which typically involved heating as the trigger to promote the second, more reluctant reaction. Mechanistic considerations as well as synthetic applications demonstrating the value of this interchangeable catalyzed sequence are presented.

Introduction

The mechanistic process of allylic ionization of leaving groups by transition metals,[1] such as Pd(0), is quite different than the oxidative addition of the same catalysts into a vinyl− or aryl−halide (or pseudohalide) bond.[2] The current accepted mechanism of allylic ionization and subsequent nucleophilic attack with stabilized anions is that both processes proceed in an anti-periplanar arrangement with respect to the metal−olefin bond.[1] This has been strongly supported by stereochemical results, i.e., retention and inversion studies.[3] Thus, with stabilized nucleophiles, such as malonate-type anions, the metal never comes into direct contact with the leaving or incoming group. In the case of cross-coupling reactions, docking of the metal onto the olefin precedes insertion into the carbon-leaving group bond (oxidative addition).[2] Oxidative addition is then followed typically by metal−metal exchange with the coupling partner and reductive elimination to yield the product.

While the reactivity profiles of the leaving groups are essentially the same for both processes, i.e., I > OTf > Br > Cl, allylic ionization is thought to be significantly faster kinetically than oxidative addition.[4] This would be relevant if both reactions were possible with the same substrate or on different substrates in the same reaction flask. Although the processes are mechanistically distinct, one could make an argument that the principal factor controlling this selectivity between the two processes is enthalpy (electronic effects). The first studies conducted on the chemoselectivity of vinylic and allylic leaving group activation by Pd was reported by Nwokogu in 1984,[5] and related studies have been published more recently.[6] These papers all report on substrates that possess both vinyl and allylic functional groups that can be activated by Pd(0). Interestingly, these reports all detail the activation of a vinyl leaving group in the presence of the allylic one, which on the surface would appear quite surprising. A more careful inspection of these reports reveals substrates that are cyclic, hindered, or both. This could lead to the conclusion that the activation of these particular vinyl groups was substrate-specific and that the demonstrated chemoselectivity was promoted principally by steric or conformational arguments, and not electronic ones. Orbital alignment to facilitate allylic ionization is extremely important.[3,6a] If the substrate cannot adopt the necessary

(1) For reviews on allylic substitution using transition metals, see (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173−1192. (b) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, England, 1982; Vol. 8, pp 799−938. (c) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley and Sons Ltd.: Chichester, England, 1995.

(2) For reviews of various cross-coupling processes, see (a) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, England, 1991; Vol. 3, pp 521−549. (b) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995**, 129−160. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (d) Heck, R. F. *Palladium reagents in organic syntheses*; Academic: New York, 1985.

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(4) (a) Ratovelomanana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917−923. (b) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 3811−3812. (c) Rossi, R.; Carpita, A.; Quirioci, M. G.; Gaudenzi, M. L. *Tetrahedron* **1982**, *38*, 631−637. (d) Semmelhack, M. F.; Brickner, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3945−3947.

(5) (a) Nwokogu, G. C. *Tetrahedron Lett.* **1984**, *25*, 3263−3266. (b) Nwokogu, G. C. *J. Org. Chem.* **1985**, *50*, 3900−3908.

(6) (a) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057−3064. (b) Yamamoto, K.; Heathcock, C. H. *Org. Lett.* **2000**, *2*, 1709−1712.

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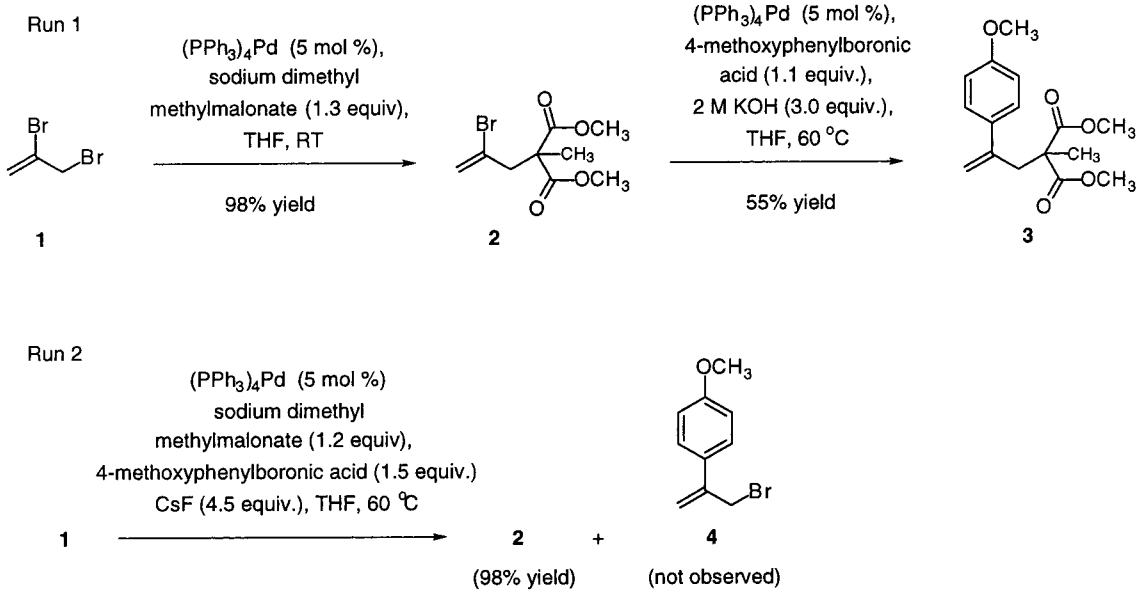
Scheme 1



antiperiplanar orientation of the metal with the leaving group, ionization does not take place. Thus, there has yet to be a study reported that definitively illustrates a preference for the activation of a vinyl leaving group over an allylic one on the basis of purely electronic considerations.

We now report that we can control routinely the chemoselectivity of Pd activation of either vinylic or allylic leaving groups interchangeably with nonsterically or conformationally biased substrates. This is achieved by altering the pK_a of the conjugate acid of the allylic leaving group on very simple 3-carbon olefin building blocks without changing the vinyl halide, which results in an "electronic switch" in reactivity. In addition to probing the mechanistic aspects of what governs the selectivity of Pd activation with multifunctionalized olefin substrates, we have set out to design a new series of small olefin building blocks that can utilize known catalysts, coupling partners, and procedures to prepare targets by either allylic substitution chemistry followed by cross-coupling or the reverse as the synthetic route demands. This will enhance the synthetic flexibility of these transition-metal-catalyzed processes, and the new olefin building blocks can be readily adopted by synthetic chemists working in the field.[7]

Results and Discussion

In Scheme 1, run 1, the allylic bromide of **1** was reacted selectively in the presence of the vinylic bromide. Compound **2** was isolated quantitatively, indicating that, under these reaction conditions, no Pd appears to be inserting into the vinyl bromine bond. In a separate operation, **2** could be converted to **3** by a Suzuki coupling at 60 °C, as there was minimal reaction at room temperature (RT). In a competition study (Scheme 1, run 2), the malonate anion and cross-coupling components were added simultaneously and the reaction was monitored by thin-layer chromatography (TLC) and ^{1}H NMR spectroscopic analysis. Allylic substitution was finished in less than 1 min with no observed cross-coupled products, i.e., **3** or **4**, at that time. However, if this reaction was left for a prolonged period, **2** gradually converted into **3**, indicating that the two processes can be set up to run in a self-controlled sequential fashion. The vinylic C−Br bond is ∼12 kcal/mol stronger than its allylic counterpart, which no doubt plays a role in the selectivity displayed by the catalyst with **1**.[8] We have demonstrated previously that the ability to control the reactivity of these two centers is very useful for synthetic applications.[7]

While the theory of microscopic reversibility states that all reactions are merely equilibria, in practice most are not by design. The example in Scheme 2 is interesting mechanistically because the phenoxide leaving group[9] in **5** is also a potential nucleophile.[10] When the cross-coupling reaction was attempted at RT, the reaction was very sluggish and **5** was returned essentially unaltered. However, when the reaction was heated to 66 °C, **5** was consumed and the desired product **6** was formed along with significant quantities of **7** and **8** (**6**:**7**:**8**, 3.3:1:1). When the reaction was performed at 50 °C, the ratio of **5**:**6**:**7**:**8** was 1:9:0.1:0, which indicated that allylic ionization of the phenoxy group could be all but eliminated by controlling the temperature. The presence of **6** coupled with the absence of **9** in the product mixture(s) indicates that, under these reaction conditions, oxidative addition of the vinyl bromide to Pd(0) was now kinetically the fastest process. Thus, we have reversed completely the reacting site for the same catalyst from the allylic site of **1** (vide supra) to the vinyl site of **5** without changing the reactivity profile of the allylic site; i.e., it is still a readily

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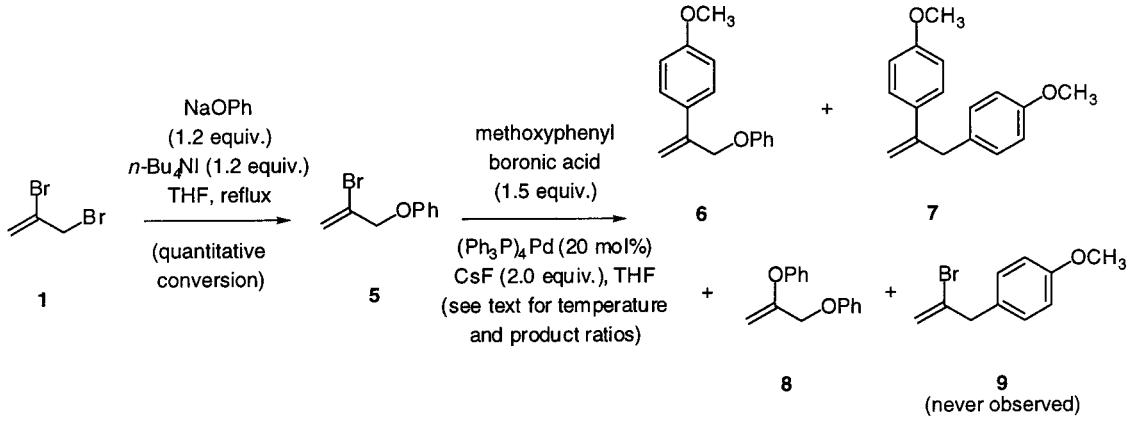
(8) Bond strength for vinyl bromide is approximately 71.5 kcal/mol; see Rahaman, A.; Raff, L. M. *J. Phys. Chem. A* **2001**, *105*, 2156−2172. Bond strength for allyl bromide is approximately 60.0 kcal/mol; see Tsang, W. *J. Phys. Chem.* **1984**, *88*, 2812−2817.

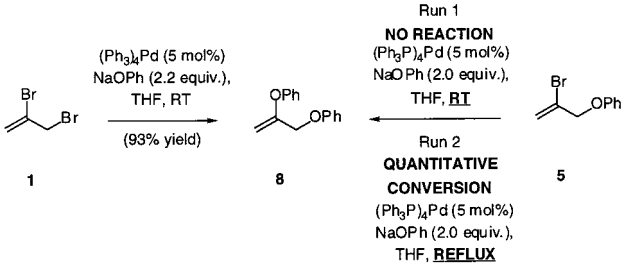
(9) For examples of Pd-catalyzed allylation reactions with a phenolate leaving group, see (a) Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 1475−1478. (b) Yamamoto, K.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 3089−3092. (c) Hutchins, R. O.; Learn, K. *J. Org. Chem.* **1982**, *47*, 4380−4382. (d) Bolitt, V.; Chaquir, B.; Sinou, D. *Tetrahedron Lett.* **1992**, *33*, 2481−2484.

(10) For examples of Pd-catalyzed allylation reaction with phenolate nucleophile, see (a) Organ, M. G.; Miller, M. *Tetrahedron Lett.* **1997**, *38*, 8181−8184. (b) Organ, M. G.; Miller, M.; Konstantinou, Z. *J. Am. Chem. Soc.* **1998**, *120*, 9283−9290. (c) Satoh, T.; Ikeda, M.; Kushino, Y.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 2662−2664. (d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815−816. (e) Kadota, J.; Katsuragi, H.; Fukumoto, Y.; Murai, S. *Organometallics* **2000**, *19*, 979−983.

Scheme 2



Scheme 3



activatable leaving group. This opens up some very interesting mechanistic studies and potential synthetic applications.

We have shown previously that when **1** is treated with 2 or more equiv of sodium phenoxide in the presence of a Pd(0) catalyst at RT, compound **8** is the only product formed (Scheme 3).[10a,b] Thus, the only way we could obtain **5** was under non-Pd-catalyzed conditions (Scheme 2). Submitting **5** to identical reaction conditions as for **1** did not provide **8** at RT (run 1, Scheme 3, no reaction). This confirmed that phenoxide was not being cross-coupled at the vinyl bromide site following allylic substitution with the first phenoxide.[11] However, consistent with the results above, when this same reaction was heated under reflux (run 2, Scheme 3), ionization of the phenoxy group was achieved leading to the formation of **8**, which precedes via initial attack of phenoxide at the C2 position of the initially formed π-allyl−Pd complex.[10a,b,e,12] This is consistent with the mechanism first proposed by Bäckvall and co-workers.[12f]

When compound **10** was reacted under Suzuki conditions,[2c] compound **11** was formed (Scheme 4, run 1). The addition of the alkyl group to the phenoxy ring was done to discourage ionization and enhance selectivity by further separating the energetics between ionization and oxidative addition. Compound **11** was then reacted subsequently under allylic substitution conditions to provide **3**. In truth, the reactions need not be done as separate transformations. In run 2, the reagents for the two steps were combined and the mixture was heated. The conversions took place in a controlled sequence, i.e., via intermediate **11** to provide **3** (followed by ^{1}H NMR spectroscopy). Thus, the reaction components under Pd(0) catalysis could assemble themselves in a predictable fashion. Therefore, we can prepare compounds resembling **3** by our choice of allylic substitution followed by cross-coupling from compound **1** or the reverse via the complimentary olefin template **10**. We are presently conducting a series of experiments to correlate leaving group ability and pK_a across a variety of substituted phenols. This will enable us to further separate the energetics of the two processes so that cross-coupling can be done with no fear of ionization; this work will be communicated in due course.

To illustrate a practical application of this reversed reactivity, consider the approach we devised recently to prepare a molecular library of approximately 1400 allylic amines for biological evaluation (Scheme 5).[13] Allylic amines are present as central motifs in molecules with diverse pharmacological properties such as Acrivastine (Semprex),[14] Flunarizine (Sibelium, Ca channel blocker),[15] and several GABA uptake inhibitors.[16]

Despite the short synthetic approach, we struggled with this route for some time for a number of reasons. Amines are among the most readily available centers of diversity, either by synthesis or from commercial sources, for the preparation of libraries of compounds for biological purposes.[17] For practical considerations, when a library is being prepared it is often best to bring an amine into the structure in the final step, which is typically when the major diversification of the pharmacophore is done. This is often accomplished by reductive amination, by amide/sulfonamide bond formation, or by noncatalyzed amine substitution chemistry.[18] Another important factor when a protonateable amine is added in the final step is that this facilitates simple "catch and release" purification with cation-exchange resins to avoid high-throughput HPLC.[19]

(11) For examples of cross-coupling oxygen-based nucleophiles, see (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395−3396. (b) Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 5413−5418.

(12) For other examples attack at the middle position of a π-allyl complex, see (a) Ephritikhine, M.; Green, M. L. H.; MacKenzie, R. E. *J. Chem. Soc., Chem. Commun.* **1976**, 619−621. (b) Hegedus, L. S.; Darlington, W. H.; Russel, C. E. *J. Org. Chem.* **1980**, *45*, 5193−5196. (c) Tjaden, E. B.; Casty, G. L.; Stryker, J. M. *J. Am. Chem. Soc.* **1993**, *115*, 9814−9815. (d) Carfagna, C.; Galarini, R.; Linn, K.; López, J. A.; Mealli, C.; Musco, A. *Organometallics* **1993**, *12*, 3019−3028. (d) Ohe, K.; Matsuda, H.; Morimoto, T.; Ogoshi, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 4125−4126. (f) Castano, A. M.; Aranyos, A.; Szabó, K. J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2551−2553. (g) Tsai, F.-Y.; Chen, H.-W.; Chen, J.-T.; Lee, G.-H.; Wang, Y. *Organometallics* **1997**, *16*, 822−823.

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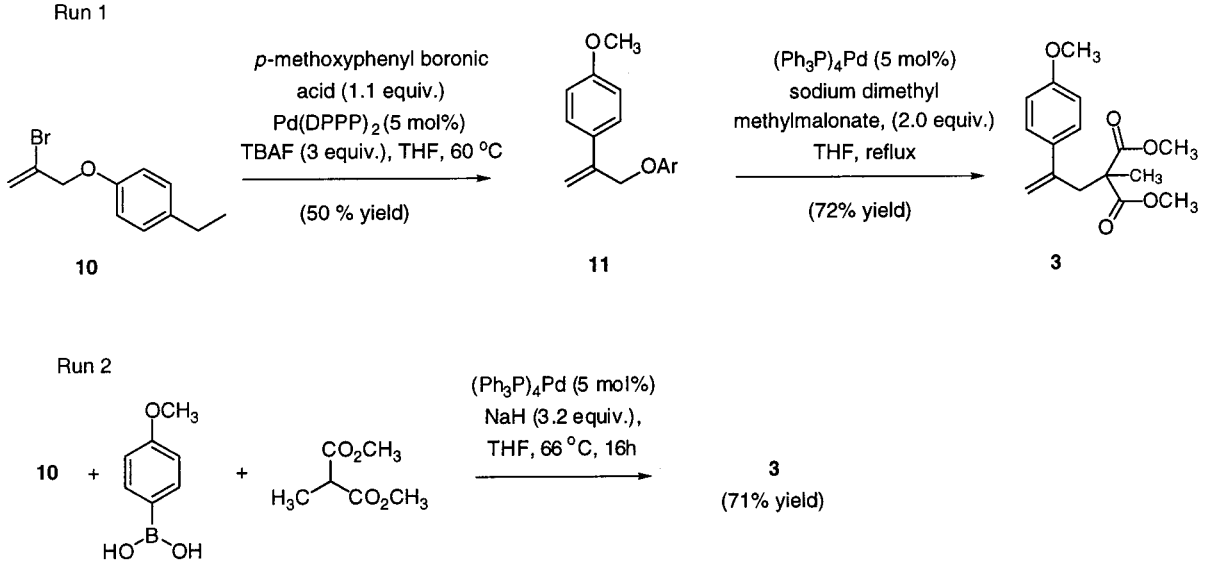
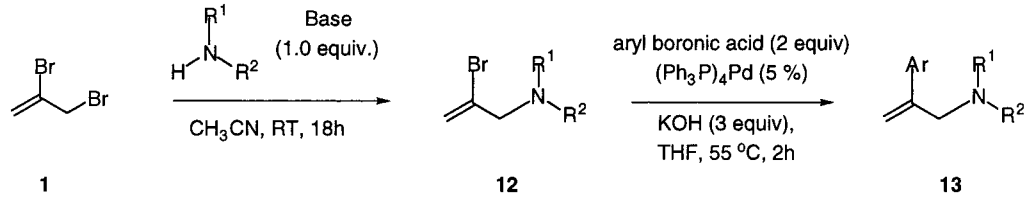
(16) Andersen, K. E.; Sorensen, J. L.; Huusfeldt, P. O.; Knutsen, L. J. S.; Lau, J.; Lundt, B. F.; Petersen, H.; Suzdak, P. D.; Swedberg, M. D. B. *J. Med. Chem.* **1999**, *42*, 4281.

(17) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937−940.

Scheme 4

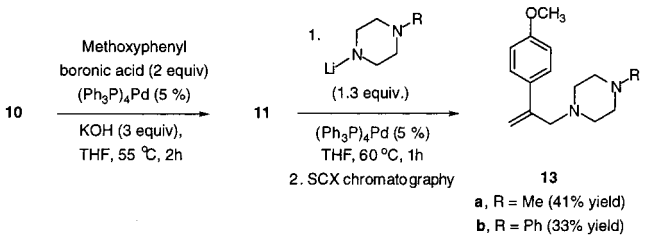


Scheme 5



However, substrates in Suzuki reactions that have an amine in their structure are a cause for concern with both the boronic acid coupling partner, which can form very strong "ate" complexes with amines, and with the Pd catalyst itself. While in practice complexation between the amines and boronic acids did not prove to be too problematic, complexation with the Pd did. Significant "blacking out" of the catalyst occurred, which was caused, presumably, by complexation of the amines in the substrate to the metal. Amines are hard σ donors that are not capable of back-bonding to support a late (soft) transition metal such as palladium. That meant we had to go with higher than desired phosphine loading with tetrakis(triphenylphosphine)-palladium(0), which complicated the high-throughput purification. However, with **10** now in hand, we have greatly simplified the approach for the preparation of libraries of **13** by taking advantage of this reversed (or switched) reactivity (Scheme 6). This seemingly simple change will significantly increase the molecular diversity that can be attained by adding the amine in the last step, while at the same time reducing the complexity of the high-throughput synthetic manipulations.

Scheme 6



While compound **8** was prepared by nucleophilic attack of phenoxide ion onto substrate **1** under Pd(0) catalysis, the ionization studies of phenoxide-based ions (e.g., **6** or **10**) led us to postulate that **8** could as well serve as an electrophilic substrate for substitution chemistry. Traditional synthon analysis for a carbonyl would place negative charge on the α-carbon, and indeed enol ether and enolate chemistry dominate nucleophilic reactions based on the carbonyl group. Treatment of **8** under standard allylic substitution conditions provided **15** via Pd π-allyl intermediate **14**, which constitutes an *umpolung* transformation (Scheme 7).[20] The phenyl enol ether moiety in **8** allows ionization of phenoxide to take place, resulting in the generation of a cation α to the masked carbonyl, which is liberated upon acid hydrolysis to give **16**. The traditional electrophilic carbonyl substrate is an α-halo ketone, which can be prepared routinely with relatively hindered ketones and substituted with nucleophiles such as amines or phenolates.[21]

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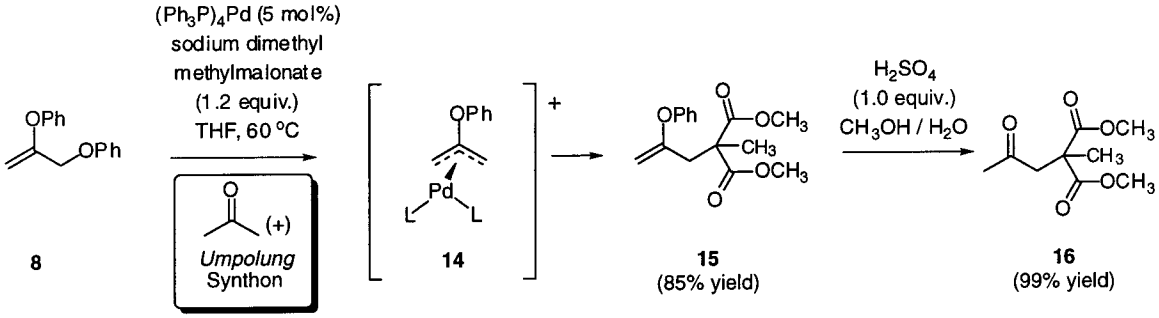
(19) (a) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193−7196. (b) Sturino, C. F.; Labelle, M. *Tetrahedron Lett.* **1998**, *39*, 5891−5894. (c) Fréchet, J. M. J.; Hagen, A. J.; Benezra, C.; Cheminat, A. *Pure Appl. Chem.* **1982**, *54*, 2181−2188. (d) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874−4881. (e) Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567−2573. (f) Chucholowski, A.; Masquelin, T.; Obrecht, D.; Stadlwieser, J.; Villalgordo, J. M. *Chimia* **1996**, *50*, 525. (g) Organ, M. G.; Dixon, C. E.; Mayhew, D.; Parks, D. J.; Arvanitis, E. A. *Comb. Chem. High Throughput Screening* **2001** (submitted for publication).

(20) For previously reported acetonylation reagents with Pd catalysis, see (a) Trost, B. M.; Gowland, W. *J. Org. Chem.* **1979**, *44*, 3448−3450. (b) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699−5700. (c) Negishi, E.-i.; Luo, F.-T. *J. Org. Chem.* **1983**, *48*, 2427−2430. (d) Schuda, P. F.; Berstein, B. *Synth. Commun.* **1984**, *14*, 293−299.

(21) Haberman, J.; Ley, S. V.; Smits, R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2421−2423.

Scheme 7

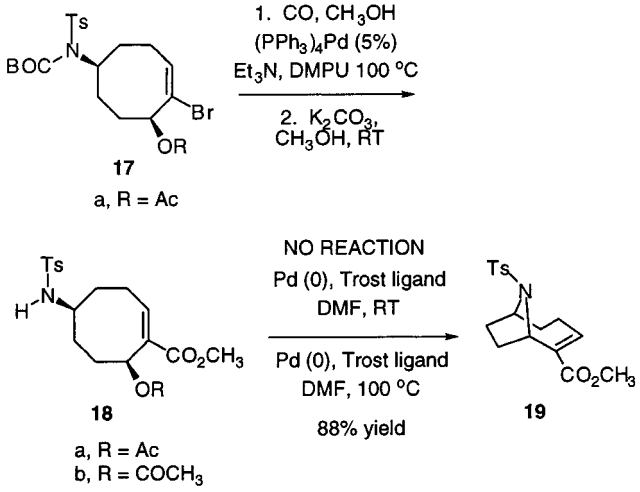


However, bromoacetone, the most relevant ketone to compare the present example with, is not commercially available (only as its dimethyl acetal at $4.00/g from Aldrich) and bromoacetone does not behave in such substitution reactions because of competing side reactions such as carbonyl addition and deprotonation. Also of note, the enolate of acetone cannot be prepared and reacted controllably with electrophiles by the "normal" synthon analysis because of spontaneous self-aldol condensation. Thus, **8** represents a practical surrogate for acetone, or its halogenated derivatives, as an *umpolung* synthon using Pd.

Summary

The experiments in this report demonstrate that olefin templates substituted with both allylic and vinylic leaving groups can be reacted selectively at either position by the same Pd(0) catalyst by tuning the leaving group ability of the allylic substituent. We have found that there is a narrow pK_a range (ca 1.50 pK_a units) for the phenols involved to maintain this pronounced selectivity with the vinyl bromide oxidative addition partner.[22] For example, *p*-nitrophenol will ionize competitively with oxidative addition, leading to undesirable mixtures.

Nwokogu[5] reported some time ago that vinyl bromides could be reacted selectively in Sonogashira couplings in the presence of an allylic carbonate or acetate. The pK_a values of the corresponding acids of these leaving groups are approximately 3 and 5, respectively. Upon reviewing the substrates studied by Nwokogu, it is unlikely that the origin of the selectivity observed in those cases is necessarily electronic. This would significantly affect the selectivity, hence the general use of these leaving groups in this competitive context. Substituents at the 2-position of an allylic substitution substrate (a bromine in this case) can affect greatly the binding of the catalyst to the olefin and the subsequent π-allyl complex formation, which undoubtedly plays some role in the observed chemoselectivity.[23] This is further exacerbated by the fact that most of the examples Nwokogu studied are quite hindered and/or cyclic. The trajectory of the approach of the metal to the olefin and the antiperiplanar alignment of the leaving group bond with the olefin−metal bond are critical to the process of allylic ionization.[1,3] Conformationally constrained structures, including especially substituted six-membered rings (which a number of the examples in Nwokogu's reports are) do not always ionize readily. These suggestions are strongly supported by the work of Trost and Oslob,[6a] who showed that the bromide of **17a** could be selectively carbonylated in the presence of the acetate. Under these vigorous conditions, they found no activation of the acetate, which led them to exchange the acetate for a carbonate, a better leaving group, for the next step. However, under "standard" allylic substitution conditions the carbonate could not be activated at all, although it did ionize when heated to 100 °C.[24]



Work by Murai's group[10e] also points strongly to the profound involvement of steric and conformational aspects in the literature cyclic examples discussed in this report. When they reacted 1-acetyl 2-chloro-2-propen-1-ol under Pd catalysis with a variety of nucleophiles, only the allylic leaving group was activated and all of the reactions reported high yields. While one must view the more sluggish vinyl chloride with some reservation when drawing conclusions, the fact that the ionization of Murai's acetate was quite facile at RT while those in the cyclic structures reported by Nwokogu and Trost do not readily ionize (if at all) suggests that the acetate is indeed electronically favored, but it is prevented from reacting do to unfavorable orbital overlap imparted by the structure of the starting materials in their studies.

The substrates that we have designed and prepared have essentially minimized, if not eliminated, steric and conformational issues from the chemoselectivity of Pd activation of the vinyl and allylic leaving groups involved. This is essential in order to provide new reagents, i.e., olefin templates, that can

(22) Results of pK_a analysis will be communicated in due course.
(23) For example, the allylic carbonate derived from carvone failed to ionize at all under Pd catalysis at room temperature, whereas the same substrate minus the methyl group on the double bond reacted completely within seconds under the same reaction conditions.
(24) In this same report, the authors designed new catalysts that facilitated ionization of the carbonate under less forcing conditions by vastly reducing the steric aspects of the bidentate ligand on Pd. This further supports the notion that ionization under more typical conditions is thwarted because of steric and/or conformational arguments of this particular substrate and others like it.

be adopted by others and used reliably. We are broadening our studies to probe these issues and to try to compartmentalize steric and electronic effects. By doing so, we anticipate the production of a series of broadly useful olefin templates whose functional groups can be activated selectively by a single catalyst in any order necessary to fulfill the synthetic requirement. We propose to do this by matching the pK_a value(s) for the allylic leaving groups with the bond strengths of the oxidative addition partners.

Experimental Section

General Procedure. All reactions were carried out under a positive atmosphere of dry nitrogen. Tetrahydrofuran (THF) was distilled from sodium benzophenone immediately prior to use. Proton NMR spectra were recorded either on a Bruker Avance spectrometer at 400 MHz or on a GE spectrometer at 300 MHz. Carbon NMR spectra were recorded either on a Bruker Avance spectrometer at 100 MHz or on a GE spectrometer at 75 MHz.

Methyl 4-Bromo-2-(carboxymethyl)-2-methylpent-4-enoate (2). To a suspension of NaH (60% in mineral oil, 290 mg, 7.2 mmol, 1.5 equiv) in THF (10 mL) was added dimethyl methylmalonate (905 mg, 6.2 mmol, 1.3 equiv). After 5 min, the resultant solution was added to a mixture of $(PPh_3)_4Pd$ (280 mg, 0.24 mmol, 0.05 equiv) and **1** (1.0 g, 4.8 mmol) in 2 mL of THF. This mixture was stirred at room temperature for 19 h, after which it was quenched with H_2O and diluted with ether. The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed in vacuo. Purification by flash chromatography (80:20 hexanes/ether) afforded 1.3 g of **2** as a colorless liquid (98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.66 (s, 1H), 5.58 (s, 1H), 3.74 (s, 6H), 3.16 (s, 2H), 1.50 (s, 3H); ^{13}C NMR [$CDCl_3$, 75 MHz, APT pulse sequence, evens up (+), odds down (−)] δ 171.7 (+), 127.2 (+), 121.9 (+), 53.1 (+), 52.8 (−), 46.1 (+), 19.4 (−).

Methyl 2-(Carboxymethyl)-4-(4-methoxyphenyl)-2-methylpent-4-enoate (3). To a solution of **2** (285 mg, 1.07 mmol, 1.0 equiv), 4-methoxyphenylboronic acid (179 mg, 1.18 mmol, 1.1 equiv), and $(PPh_3)_4Pd$ (62 mg, 0.05 mmol, 0.05 equiv) in 7 mL of THF was added 1.34 mL of a 2 M KOH solution. After stirring at 60 °C for 3 h, ether was added and the mixture was partitioned. The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo. Flash chromatography (70:30 hexanes/ether) provided 172 mg of **3** as a clear oil (55% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.20 (s, 1H), 5.03 (s, 1H), 3.80 (s, 3H), 3.51 (s, 6H), 3.14 (s, 2H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 159.1, 143.8, 134.0, 127.9, 117.0, 113.4, 55.3, 53.4, 52.3, 40.6, 19.9.

1-[(2-Bromoprop-2-enyl)oxy]benzene (5). To a suspension of NaH (560 mg, 14 mmol, 1.4 equiv) and *n*-Bu_4NI (4.35 g, 12 mmol, 1.2 equiv) in THF (25 mL) was added dropwise a solution of phenol (1.13 g, 12 mmol, 1.2 equiv) in THF (25 mL). The resultant suspension was heated at 65 °C until complete dissolution of the solids occurred. 2,3-Dibromoprop-1-ene (**1**) (1.93 g, 10 mmol, 1 mL) was then added and the reaction mixture was stirred for 17 h before being quenched with H_2O. The mixture was diluted with ether, 5 mL of a 2 M NaOH solution was added, and the layers were separated. The organic phase was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo. Purification by flash chromatography (95:5 hexanes/ether) afforded 1.51 g of **5** as a colorless liquid (98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (d, J = 8.0 Hz, 2H), 7.04 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 8.0 Hz, 2H), 6.05 (s, 1H), 5.72 (s, 1H), 4.68 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.9, 129.6, 127.3, 121.7, 117.7, 115.0, 71.7; HRMS calcd for $C_{18}H_{19}O_6N - 2H^+$ (M − 2H$^+$) 211.9865, found 211.9837.

Reaction of Compound 5 under Suzuki Conditions (Products 6, 7, and 8). This reaction was performed at a number of temperatures under these general conditions (see text and reaction schemes for specific temperatures and product ratios): Into a 10 mL round-bottom flask (rbf) was added 3 mL of THF, CsF (57 mg, 0.57 mmol, 2.0 equiv), (4-methoxyphenyl)boronic acid (52 mg, 0.35 mmol, 1.5 equiv), and **5** (50 mg, 0.23 mmol, 1.0 equiv). After 53 mg of $(PPh_3)_4Pd$ (46 mmol, 0.2 equiv) was added, the reaction was heated to the desired temperature and the reaction's progress was monitored by TLC. When the reaction was deemed complete, it was cooled and diluted with ether, and 5 mL of H_2O was added. The phases were separated and the organic layer was dried over anhydrous $MgSO_4$. Following filtration, the solvent was removed in vacuo and the residue was purified by flash chromatography (95:5 hexanes/ether).

1-(Phenoxy)-2-(4-methoxyphenyl)prop-2-ene (6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, J = 8.0 Hz, 2H), 7.30 (m, 2H), 6.98 (m, 3H), 6.90 (d, J = 8.0 Hz, 2H), 5.55 (s, 1H), 5.40 (s, 1H), 4.89 (s, 2H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5, 158.7, 142.4, 130.8, 129.5, 127.2, 121.0, 115.0, 113.9, 113.3, 70.0, 55.3.

1,2-Di(4-methoxyphenyl)prop-2-ene (7). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 5.40 (s, 1H), 4.94 (s, 1H), 3.85 (S, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 158.0, 146.5, 133.3, 131.7, 129.8, 127.3, 113.8, 113.6, 112.7, 55.2 (two coincident peaks), 40.9.

1,2-Diphenoxy-2-propene (8). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.25 (m, 4H), 7.17−7.04 (m, 3H), 7.02−6.93 (m, 3H) 4.63 (s, 2H), 4.59 (d, J = 2.2 Hz, 1H), 4.24 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.43, 158.19, 155.02, 129.64, 129.43, 124.30, 121.23, 120.65, 115.01, 91.31, 67.46; HRMS calcd for $C_{15}H_{14}O_2$ [M]$^+$ 226.0994, found 226.0995.

1,2-Diphenoxy-2-propene (8). Into a 10 mL test tube were added THF (1 mL), NaH (60% dispersion in mineral oil, 3.0 equiv, 36.2 mg, 1.50 mmol), and 141 mg of phenol (3.0 equiv, 1.50 mmol), which was added slowly to control H_2 gas evolution. To this homogeneous solution was added 29.0 mg of $(PPh_3)_4Pd$ (0.05 equiv, 0.025 mmol) followed by **1** (100 mg, 0.50 mmol), and the mixture was stirred for 16 h. The suspension was then diluted with 40 mL of ether and 10 mL of water. The organic layer was separated and dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. Purification by flash chromatography (straight pentane) afforded 104 mg of **8** as a clear oil (78% yield).

1-[(2-Bromoprop-2-enyl)oxy]-4-ethylbenzene (10). To a solution of 4-ethylphenol (2.93 g, 24 mmol, 1.2 equiv) in THF (50 mL) was added NaH (60% mineral oil suspension, 0.88 g, 22 mmol, 1.1 equiv) in small portions. After gas evolution had ceased, 4.06 g of **1** (20 mmol, 1 equiv) was added. The reaction mixture was stirred at 60 °C for 16 h, quenched with brine, and diluted with ethyl acetate, and the phases were separated. The organic phase was washed with 2 M aqueous NaOH, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed in vacuo. Purification by flash chromatography (80:20 hexanes/ether) afforded 4.8 g of **10** as a pale yellow liquid (99% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 6.02 (s, 1H), 5.68 (s, 1H), 4.64 (s, 2H), 2.63 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.9, 137.0, 128.8, 127.5, 117.5, 114.9, 71.9, 28.0, 15.8.

1-[(4-Ethylphenyl)oxy]-2-(4-methoxyphenyl)prop-2-ene (11). To a solution of **10** (0.48 g, 2.0 mmol) in THF (2 mL) was added bis-[1,3-(diphenylphosphino)propane]palladium(0) (93.0 mg, 0.1 mmol, 0.05 equiv). The orange solution was heated to 45 °C for 1 h, after which a 1 M solution of *n*-Bu_4NF in THF (6 mL, 0.6 mmol, 3 equiv) containing (4-methoxyphenyl)boronic acid (0.33 g, 2.2 mmol, 1.1 equiv) was added dropwise via cannula. Upon addition, the reaction mixture became clear and it was heated to 60 °C for 1.6 h, at which time it was quenched with H_2O. Ether and 2 M aqueous NaOH were added and the layers were separated. The organic phase was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo. Purification by flash chromatography (90:10 hexanes/ether) afforded 271 mg of **11**

as colorless crystals (50% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.5 Hz, 4H), 5.53 (s, 1H), 5.38 (s, 1H), 4.85 (s, 2H), 3.82 (s, 3H), 2.62 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5, 156.8, 142.5, 136.8, 130.9, 128.7, 127.2, 114.9, 113.9, 113.2, 70.2, 55.3, 28.0, 15.8.

2-(4-Methoxyphenyl)-3-(4-methylpiperazinyl)prop-1-ene (13a). To a solution of 4-methylpiperazine (36.0 mg, 0.36 mmol, 1.3 equiv) in THF (2 mL) was added *n*-BuLi (1.6 M solution in hexanes, 0.240 μL, 0.38 mmol, 1.4 equiv). After 10 min, this was added to a solution of **11** (74.0 mg, 0.28 mmol, 1.0 equiv) and $(PPh_3)_4Pd$ (16.0 mg, 0.014 mmol) in THF (2 mL) that was stirred at 65 °C for 30 min. The reaction mixture became red instantly, then brown, and it was further stirred at 65 °C for 7 h before being quenched with H_2O. Ether was added along with 2 M NaOH, and the product partitioned into the organic layer. The organic phase was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo. The crude product was dissolved in 1 M AcOH solution (3 mL) and loaded onto an SCX column (2 × 500 mg, Whatman). The resin was washed with MeOH and CH_2Cl_2. Elution with a 2 M NH_3 solution in MeOH (Aldrich) afforded 36 mg of **13a** (41% yield) together with the excess 4-methylpiperazine. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.39 (s, 1H), 5.14 (s, 1H), 3.80 (s, 3H), 3.31 (s, 2H), 2.55−2.31 (m, 8H), 2.29 (s, 3H).

2-(4-Methoxyphenyl)-3-(4-phenylpiperazinyl)prop-1-ene (13b). To a solution of 4-phenylpiperazine (54 mg, 0.33 mmol, 1.2 equiv) in THF (2 mL) was added *n*-BuLi (1.5 M solution in hexanes, 0.36 mmol, 0.240 mL, 1.3 equiv). After 10 min, this was added to a solution of **11** (740 mg, 0.28 mmol, 1.0 equiv) and $(PPh_3)_4Pd$ (16.0 mg, 0.014 mmol, 0.05 equiv) in THF (2 mL) that was stirred at 65 °C for 30 min. The reaction mixture became instantly red-brown and was stirred at 65 °C for 1 h before being quenched with H_2O. Ether was added along with 2 M NaOH, and the product partitioned into the organic layer. The organic phase was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo. Purification by flash chromatography (70:30 hexanes/ether) afforded 38 mg of **13b** as colorless liquid (33% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, J = 8.5 Hz, 2H), 7.27−7.34 (m, 3H), 6.92 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 5.45 (s, 1H), 5.20 (s, 1H), 3.82 (s, 3H), 3.39 (br s, 2H), 3.19 (br s, 4H), 2.59 (s, 4H).

Methyl 2-(Carboxymethyl)-2-methyl-4-phenoxypent-4-enoic Diacid (15). To a suspension of NaH (60% in mineral oil, 84.0 mg, 2.1 mmol, 1.4 equiv) in THF (2 mL) was added dimethyl methylmalonate (1.8 mmol, 240 μL, 1.2 equiv) dropwise. After 5 min, this was added to a solution of **8** (339 mg, 1.5 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (86.0 mg, 0.07 mmol, 0.05 equiv) in THF (2 mL). The solution was heated to 50 °C, at which point it became red and then gradually turned yellow over time. The reaction mixture was stirred at 60 °C for 17 h before being quenched with water and diluted with ether and 2 M aqueous NaOH. The phases were separated; the organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo. Purification by flash chromatography (70:30 hexanes/ether) afforded 354 mg of **15** as colorless crystals (85% yield). Mp 45−48 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (t, J = 8.0 Hz, 2H), 7.13 (t, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 4.14 (s, 1H), 3.94 (s, 1H), 3.72 (s, 6H), 2.94 (s, 2H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 158.9, 154.7, 129.6, 124.5, 121.2, 91.1, 52.5, 40.1, 19.7; HRMS calcd for $C_{15}H_{18}O_5$ $[M]^+$ 278.1139, found 278.1154. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.30; H, 6.74.

Methyl 2-(Carboxymethyl)-2-methyl-4-oxopentanoate (16). To a solution of **15** (140 mg, 0.5 mmol) in MeOH/H_2O (5.0/0.5 mL) was added concentrated H_2SO_4 (25 μL, 0.5 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 2 h before being quenched with H_2O and partitioned between ether and brine. The organic phase was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo. No purification was required and the reaction returned 124 mg of **16** as a pale yellow liquid (99% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.72 (s, 6H), 3.09 (s, 2H), 2.14 (s, 3H), 1.51 (s, 3H).

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Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra for all compounds prepared in this study (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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