Enantioselective Catalysis

How to cite:
International Edition: doi.org/10.1002/anie.202108336
German Edition: doi.org/10.1002/ange.202108336

Enantioselective Lactonization by π-Acid-Catalyzed Allylic Substitution: A Complement to π-Allylmetal Chemistry

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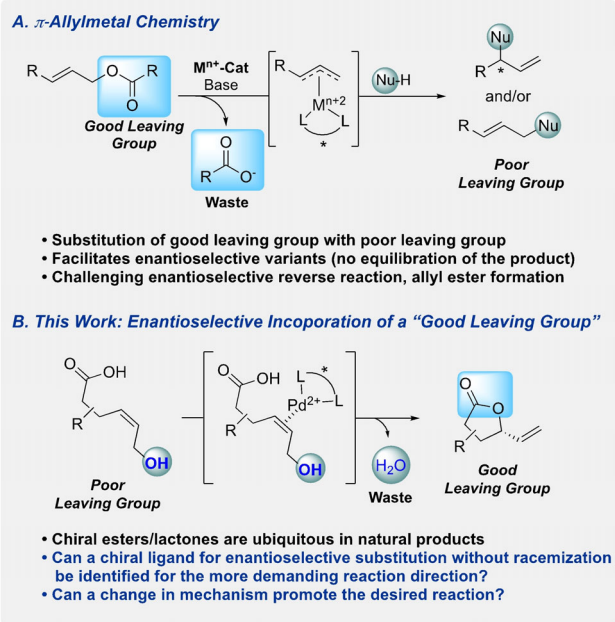
Abstract: *Asymmetric allylic alkylation (AAA) is a powerful method for the formation of highly useful, non-racemic allylic compounds. Here we present a complementary enantioselective process that generates allylic lactones via π-acid catalysis. More specifically, a catalytic enantioselective dehydrative lactonization of allylic alcohols using a novel Pd^{II}-catalyst containing the imidazole-based P,N-ligand (S)-StackPhos is reported. The high-yielding reactions are operationally simple to perform with enantioselectivities up to 99 % ee. This strategy facilitates the replacement of a poor leaving group with what would ostensibly be a better leaving group in the product avoiding complications arising from racemization by equilibration.*

Enantioselective catalysis has continued to evolve and serve as a powerful tool for the preparation of enantioenriched molecules such as pharmaceuticals, agrochemicals, and fine chemicals.[1] Among these transformations, catalytic asymmetric allylic alkylation has been highly successful, owing in part to the broad range of substrate types and nucleophilic partners that can be used to generate a plethora of enantioenriched compounds suitable for further functionalization.[2] Most of these methods, including the pioneering work by Tsuji and Trost, utilize an allylic compound bearing a good leaving group (ester, carbonate, etc.) to form an electrophilic π-allylmetal intermediate for reaction with a nucleophilic partner in the construction of C–X and C–C bonds (Scheme 1 A).[3] Although, these activated alcohols require an additional synthetic step, activation facilitates ionization under mild conditions and helps differentiate the electrophile from its nucleophilic partner. Perhaps more importantly, for enantioselective transformations the substrate is more easily ionized than the product, so a kinetically formed non-racemic product does not suffer racemization by thermodynamic equilibration.

Considering that esters and lactones are ubiquitous in biologically active compounds,[4] preparation by AAA would also be extremely useful, but this is problematic because they are easily ionized under the conditions and are therefore prone to racemization.[5] Trost notes that the problem is "more severe than it appears at first glance"[5a] and consequently ester-forming Pd-AAA is scarce. Similarly, with Ir-AAA, Helmchen demonstrates time dependent loss of *ee*.[5b] Alternatively, Overman employed a Pd^{II}-catalyst with allylic trichloroacetimidates; but, with this activating group, the uncatalyzed reaction is problematic for nucleophiles with pK_a's below 4. In these reactions, with acidic substrates, low yields and *ee*'s of the desired products are observed and the major products are the linear trichloroacetimidate-substitution product.[6e]



Scheme 1. Allylic Substitution.

As esters are the substrates for AAA, a potential strategy to overcome these issues might be to effect a reverse reaction, but this would necessitate ionization of a poor leaving group and result in the incorporation of a good leaving group. Interestingly, alcohols have been used as starting materials for AAA,[7] but this typically requires cation stabilizing substituents[8] or acidic additives to facilitate π-allylmetal formation.[9] While this provides entry to the reaction manifold from the traditional product side, it does not readily enable the enantioselective formation of allyl ester products. Kitamura reported an elegant enantioselective approach employing a bifunctional Ru-catalyst that mediates π-allylmetal formation by proton transfer avoiding the necessity for activated substrates.[10] While the process requires 100 °C, presumably protonation and ionization of the allylic alcohol substrate is more facile than it is on the lactone product. Although the reaction proceeds via a π-allylmetal intermediate, differentiation attributable to a change in mechanism suggests that

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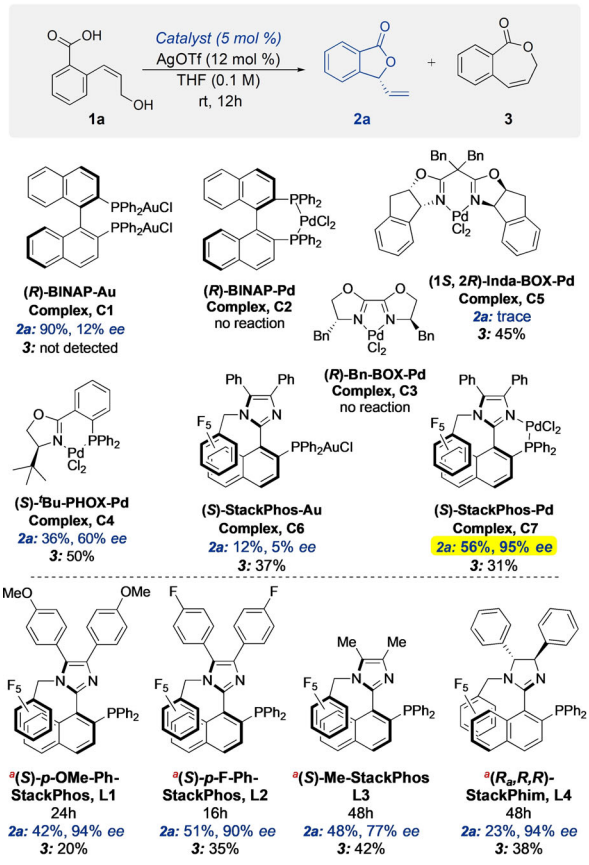
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/anie.202108336.

other enantioselective processes might be possible under mild conditions if an alternative pathway could be accessed.

Mechanistically, if the π-allylmetal could be avoided, racemization due to leaving group ability should not be detrimental to enantioselective processes and an enantioselective reverse reaction, of sorts, should be possible (Scheme 1 B). Our group has a longstanding interest in dehydrative transformations[11] and we reported dehydrative allylic lactonization with Au^{I}- and Pd^{II}-catalysts.[11e] The reaction proceeded best under "ligandless" conditions using $(CH_3CN)_2PdCl_2$. Added ligand such as phosphine or even substoichiometric amounts of CH_3CN completely shut down the reaction and ligand inhibition is problematic to an enantioselective variant. Despite this challenging issue, we reasoned that a successful reaction would be useful from a synthetic standpoint, atom- and step-economical[12] and also desirable from a green chemistry perspective.[8c] Herein we detail our studies and report a catalyst system that is both high yielding and highly enantioselective under mild conditions.

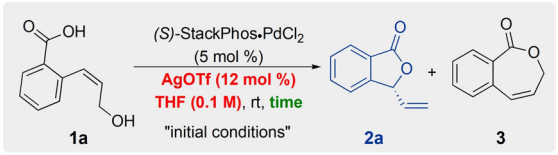
The enantioselective synthesis of 3-vinyl phthalides and butenolides is of interest due to their potential as synthons[13] towards an array of bioactive compounds.[4] To initiate the study, we selected **1a** for catalyst screening (Scheme 2). Initial trials focused on the use of Au- and Pd-complexes with *P,P*-, *N,N*-, and *P,N*-ligands and AgOTf as a halide scavenger. Consistent with the observations noted above, using Pd^{II}-complexes with *P,P*-ligands **C2,3,5** none of the desired product **2a** was formed. With the di-gold complex **C1**, **2a** was formed but in low *ee* (12%). Much to our surprise, with the C_1-symmetric *P,N*-ligand **C4**, **2a** was formed in a 36% yield and 60% *ee*, a marked improvement. However, **3** was the major product, presumably formed by a Lewis-acidic mechanism.[11e] Since PHOX is a *P,N*-ligand, a Pd-complex of our imidazole-based ligand (*S*)-StackPhos[14] was prepared and employed in the reaction to yield **2a** in 56% and remarkably 95% *ee*. With this excellent selectivity and reversal in the **2a**:**3** ratio, other StackPhos-based catalysts were explored in an attempt to improve the chemoselectivity. It should be noted that the (*S*)-ligand was used here, but both enantiomers are readily available. The corresponding Au^{I}-complex **C6** was ineffective, and no other ligand congeners provided any significant improvement, so further optimization would be needed.

StackPhos has not been used with metals other than Cu[14] and its efficacy in this Pd-catalyzed transformation is noteworthy as it seems to be uniquely suited for the reaction. With this initial high *ee* result in hand, an optimization was undertaken to minimize the formation of **3** (Table 1). During initial experiments, it was observed that the reaction did not proceed without AgOTf, 5 mol% resulted in complete loss of the reactivity (entry 2) and using solely AgOTf



Scheme 2. Catalyst Screening. [a] $PdCl_2(CH_3CN)_2$ and ligand were premixed before the reaction.

Table 1: Optimization Studies.[16]



entry	deviation	*t*	*ee* [%]	Yield **2a** [%][a]	Yield **3** [%][a]
1	none	12 h	95	56	31
2	AgOTf (5 mol%)	36 h	–	0	trace
3	No Pd catalyst, AgOTf (10 mol%)	12 h	–	0	10
4	$AgBF_4$ (12 mol%)	12 h	60	19	0
5[b]	THF (0.05 M)	36 h	–	12	3
6	THF (0.2 M)	18 h	93	62	25
7[b]	THF (0.1 M), MS 4 Å	18 h	n.d.	5	1
8	acetone (0.1 M)[c]	6 h	96	59	12
9	acetone (0.1 M)[c] H_2O (0.5 equiv)	6 h	98	82	6
10[d]	acetone (0.1 M)[c] H_2O (0.5 equiv)	7 d	99	77	9
11[e]	acetone (0.1 M)[c] H_2O (0.5 equiv)	28 h	99	81	6

[a] Isolated yield.; [b] Yield determined by ^{1}H NMR; [c] Distilled acetone; [d] $T=-25$ °C; [e] $T=0$ °C.

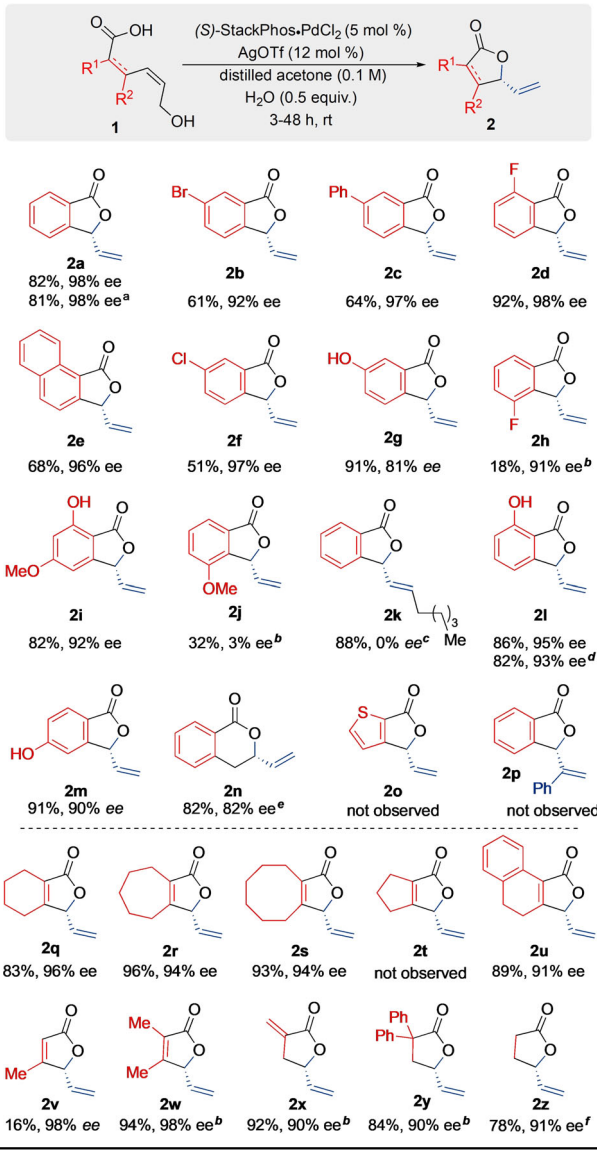
provided a 10% yield of **3**, but only after a prolonged reaction time (entry 3). Several other salts were screened but AgOTf proved optimal.[15,16] These data (no reaction without a Ag-salt and entries 1–4) suggest that dicationic-Pd^{II} is required and AgOTf likely improves the π-acidity.[15] Further experiments on the solvent showed that molecular sieves diminished the reactivity (entry 7) and, after an extensive solvent screen,[16] it was found that use of distilled acetone with 0.5 equiv H_2O struck an excellent balance between reactivity and selectivity to provide **2a** in 82% yield and 98% *ee* (entry 9). These conditions were deemed optimal. At this stage, two additional experiments should be mentioned. Firstly, it should be noted that the corresponding *trans*-substrate does not function in the reaction. Perhaps more importantly, when non-racemic product **2a** was subjected to a Pd^0-catalyst, rapidly racemization was observed, consistent with our expectations.[16,17]

The substrate scope was explored to probe generality (Table 2). A variety of substituted benzoic acids with varying electronic and steric properties were competent in the lactonization process, providing access to phthalides in good to excellent yields and *ee*'s with minimal exception. Substrates with both EWGs and EDGs functioned quite well to provide the products in excellent *ee* (**2b–g,i,l,m**). In addition to small scale experiments, the reaction was also carried out on the gram scale with **2a** and 1 mmol scale with **2l**, and both were formed in comparable yield and *ee*. This range of substrates is particularly attractive since phthalides with EDGs are present in most of the natural products of the family.[4e] Additionally, it has been reported that EWGs on the phthalide enhance the biological activity.[4f] It should also be noted that the method doesn't suffer from the same pK_a requirements as the Overman trichloroacetimidate method[6e] and more acidic substrates like the salicylic acid derived-substrates leading to **2i** and **2e** functioned well in the reaction. Despite this, some limitations are as follows: substrates with 5-substitution (**2j**), a fused thiophene (**2o**), as well as a substituted olefin (**2p**) were not tolerated. A substituted allyl alcohol was reactive, and provided **2k** in 88% yield, but a racemic substrate was employed, and this led to racemic product signifying that a π-allyl is not formed. It was also possible to form a 6-membered lactone **2n**, but further optimalization will be needed to increase the selectivity.

In addition to phthalides, the scope was expanded to γ-lactones widely found in terpenes and alkaloids such as the guaianolides and others.[4a,18] The reaction functions particularly well for fused α,β-unsaturated γ-lactones (**2q–s,u**), all exhibiting >90% *ee*. Introduction of a CH_3 at the α and β positions of the aliphatic acid resulted in the nearly optically pure (98% *ee*) γ-butenolide **2w** which is an important plant germination signalling molecule.[19] In addition, **2x** containing a highly electrophilic exomethylene moiety was isolated in 78% and 90% *ee*, but this required additional optimization. This is particularly significant since it is prone to racemization.[20]

These data demonstrate that it is possible to identify a catalyst system to replace a poor leaving group in an allylic substrate and enantioselectively form a product containing an ostensibly better leaving group without racemization. The

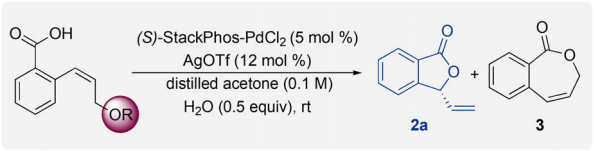
Table 2: Substrate scope.[16]

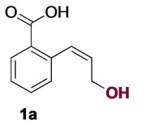
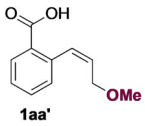
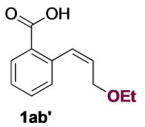
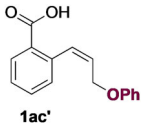
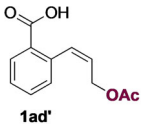


[a] 1 g scale; [b] Solvent = distilled MeOAc (0.1 M) at rt; [c] Racemic allylic alcohol substrate employed. [d] Reaction carried out at 1 mmol scale. [e] Solvent = distilled acetone:TFE (4:1, 0.1 M); [f] Solvent = distilled MeOAc (0.1 M) at 0 °C.

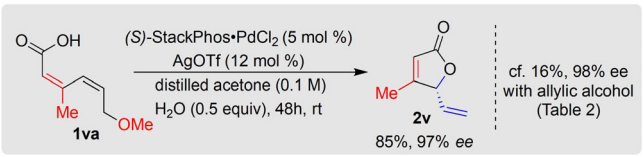
substrates described above have utilized a hydroxyl group as a leaving group and we wondered how the reaction might function with alternative, and perhaps better leaving groups.[3a,21] To this end, substrates **1aa′**–**1ad′** were prepared and subjected to the conditions. As can be seen in Table 3, and as would be expected, these substrates completely suppressed formation of **3** and **2a** was produced exclusively, albeit with an erosion of the enantioselectivity. The reactivity of alkoxyl substrates **1aa′** and **1ab′** (entries 2,3) was decreased and required 48 hours to proceed to completion but **1ac′** and **1ad′** showed only partial conversion after this prolonged reaction time (entries 4,5). It should be noted that analyses of the reaction mixtures show only product and unreacted starting material, with no other by-products.

Table 3: Leaving group studies.

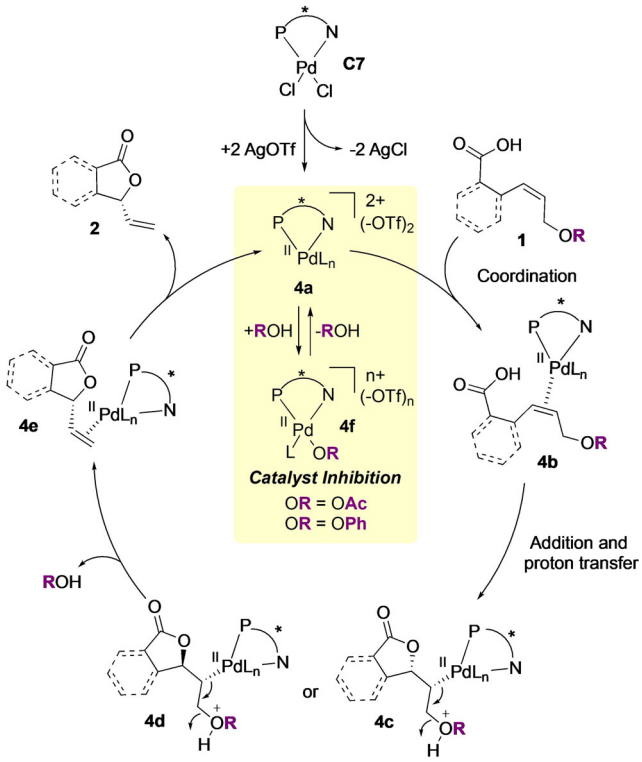


entry	substrate	*t* [h]	Yield **2a** [%]	*ee* [%]	Yield **3** [%]
1	 **1a**	6	82	98	6
2	 **1aa'**	48	90	91	0
3	 **1ab'**	48	90	91	0
4	 **1ac'**	48	17	91	0
5	 **1ad'**	48	55	91	0

Considering these results, we envisioned that allylic ethers could serve as alternative substrates when the undesired 7-membered lactone is predominant or when the synthesis of the corresponding alcohol substrate is challenging. To briefly probe this, we considered **1v** where a low yield of the **2v** was observed due to the competing direct lactonization (Table 2). Instead of the allylic alcohol, the methyl ether **1va** was prepared and exposed to the reaction conditions. In this case, **2v** was formed in 85% yield and 97% *ee*, overcoming any issues of the previous substrate.



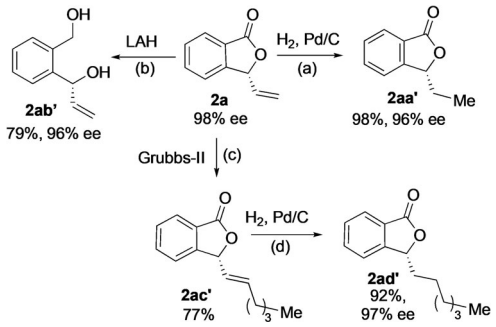
While alkoxides functioned well in the reaction, it was curious that substrates employing phenoxide and acetate as leaving groups suffered a drastic reduction in reactivity. With acetate, even though it is a good leaving group for π-allylpalladium chemistry, after 48 h <60% conversion was observed. In contrast, with -OH as leaving group, dehydrative cyclization proceeds to completion in the presence of a Pd^{II}·StackPhos catalyst at temperatures as low as −25 °C (Table 1, entries 9–11). It seems likely that this difference is correlated to the pK_a of the conjugate acid of the leaving group and the ability of the leaving group to act as a ligand. It is proposed that the active catalyst **4a** is formed in situ from **C7** with 2 equiv AgOTf (Scheme 3). The catalyst likely maintains a +2 oxidation state throughout the process and



Scheme 3. Plausible mechanism.

the π-acidic Pd-species **4a** activates the π-bond of the allylic alcohol to form the complex **4b** before addition and dehydration to form **4e** with release of ROH. Decomplexation then yields **2** and regenerates the catalyst. It is probable that, when liberated, acetate and phenol, which are better ligands for Pd than H_2O and alcohol,[3a,20] coordinate to **4a** and form a species such as **4f**, inhibiting the catalyst to produce a much slower overall reaction with incomplete conversion. At the moment, it is unclear whether the carboxylic acid in **4b** is coordinated to the metal. The coordinated species could undoubtedly be present and would likely dictate *syn*- or *anti*-addition leading to **4c** or **4d**, but it is unclear if this interaction is productive. Further experiments addressing this are underway and will be reported in due course.

The reaction products contain a synthetically useful lactone ring and a vinyl group strategically located on the ring system that we envision will be useful for subsequent transformations and further functionalization. This was briefly explored with some preliminary experiments and it was found that **2a** can be efficiently reduced to alkyl product **2aa′** and transformed into a synthon for fused γ-pyran lactones, diol **2ab′**, by LAH reduction.[22a] Furthermore, the chain was extended and reduced by metathesis and hydrogenation of **2a** to afford 3-n-butylpthalide-edaravone hybrid **2ad′** in good yield.[22b] It should be noted that only minimal



Scheme 4. Further Synthetic Transformations. Reaction conditions: a) H_2 (1 atm), Pd/C (10 wt%), THF, rt, 24 h. b) $LiAlH_4$, 0 °C—rt, 6 h. c) 1-hexene, Grubbs-II, DCM, reflux, 12 h. d) H_2 (1 atm), Pd/C (30 wt%), THF, rt, 16 h.

change in *ee* was observed and other transformations could be envisioned.[4e,11e]

In conclusion, we have reported an enantioselective π-acid catalyzed allylic substitution for the formation of lactones. This method, whereby a substrate with a poor leaving group delivers a product containing a better leaving group, provides a complementary approach to the venerable enantioselective π-allyl metal chemistry that has proven so useful to the community. By engaging the allylic substrates in an alternative mechanism, the process is able to avoid the complications of traditional π-allylmetal chemistry arising from racemization of the product through a thermodynamic equilibration that proceeds via an ionization/recombination pathway. Furthermore, the method does not appear to have the same pKa limitations as the trichloroacetimidate method. The reactions are high yielding, enantioselective, chemoselective, operationally simple to perform, and provide heterocycles with a synthetically useful vinyl group strategically located on the ring system that facilitates further transformations for target-oriented synthesis. Interestingly, substrates bearing the traditional allylic acetate leaving group can undergo a highly selective reaction with this catalyst system, but the reaction is very slow, likely due to catalyst inhibition after release of acetate. The mechanistic details and expansion of the methodology, including additional synthetic applications, are under further study in our laboratories.

Acknowledgements

The authors thank the University of Florida and The National Science Foundation (CHE-1900299) for their generous support of our programs. Mass spectrometry instrumentation was sup-ported by a grant from the National Institutes of Health (S10 OD021758-01A1).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: allylic compounds · enantioselectivity · lactones · StackPhos · π-acid catalysis

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Manuscript received: June 23, 2021
Accepted manuscript online: August 22, 2021
Version of record online: ■■ ■■, ■■■■

Communications

Enantioselective Catalysis

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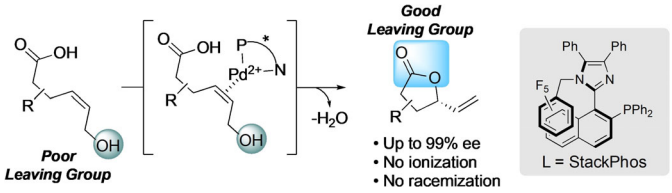
Enantioselective Lactonization by π-Acid-Catalyzed Allylic Substitution: A Complement to π-Allylmetal Chemistry



A highly enantioselective lactonization of unactivated allylic alcohols is reported under mild conditions. The transformation is catalyzed by a Pd^{II}·StackPhos complex and facilitates the substitution of a poor leaving group with what would ostensibly be a better leaving group in the product without selectivity issues arising from racemization.