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Pd(0)-catalyzed Chemo-, Diastereo- and Enantioselective α-Quaternary Alkylation of Branched Aldehydes

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ABSTRACT: Quaternary carbon stereocenters are ubiquitous in a wide variety of organic compounds and drug molecules. Highly enantioselective construction of such quaternary carbon centers poses a singular challenge due to the steric repulsion between the four different carbon substituents. Herein, we report a novel strategy to control the enantioselective construction of chiral α-quaternary aldehydes from racemic α-branched aldehydes. Distinct from the established chiral α-quaternary aldehydes synthesis, this project employed a chiral π-ally-Pd complex neighboring to the enolate to determine both the enantio- and diastereoselectivity. The synthetic utility of the products has been highlighted by a series of derivatizations and the potential of this

method extended to the synthesis of chiral α-quaternary ketones. Furthermore, this reaction exemplifies the themes of step and atom economy, in addition to the principles of diversity-oriented synthesis.

INTRODUCTION

Construction of quaternary carbon stereocenters remains a very challenging but important endeavor for modern synthetic chemistry due to its prevalence in numerous natural products and pharmaceuticals.[1] Although synthetic chemists have made tremendous progress in developing novel methodologies to form quaternary carbon centers, this still remains a daunting challenge for access to many areas of chemical space.[2] From the synthetic perspective, it is important to introduce transformable functionalities into the structure of a synthetic intermediate for further modification, instead of merely preparing an optical pure quaternary carbon centers. Among various functionalities, the formyl group plays a vital role in organic syntheses.[3] Additionally, aldehydes bearing all-carbon α-quaternary centers constitute a vital structural motif in a great number of biologically active natural products. For other synthetic targets, a formyl group bearing an α-quaternary center conveniently serves an intermediate for further transformation (Figure 1).[4]

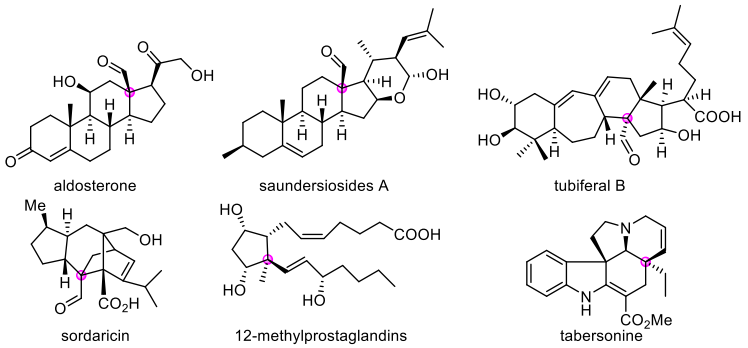
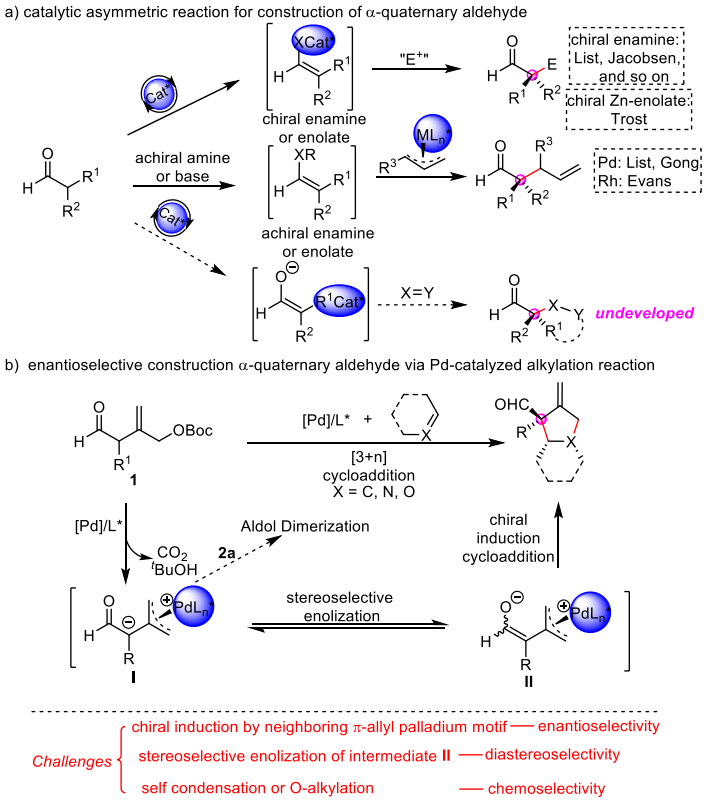


Figure 1. Representative bioactive and natural products containing α-quaternary aldehydes or converting from α-quaternary aldehydes.

At present, only limited types of catalytic asymmetric reactions are known to facilitate the formation of α-quaternary aldehydes from readily available α-branched aldehydes. With the recent advancement of organocatalysis,[5] some elegant methods have been disclosed for the direct enantioselective α-allylation or α-alkylation of aldehydes to prepare quaternary stereocenters by means of an S_N2 mechanism,[6] or an S_N1 mechanism with stabilized carbocations.[7] A chiral amine was employed as the catalyst to form the chiral enamine intermediate, which could efficiently prevent the aldol-dimerization pathway and also enable chiral induction for nucleophilic attack. In 2018, our group demonstrated a versatile enantioselective stereodivergent process to access acyclic α-quaternary aldehydes using Zn-ProPhenol catalysis (Scheme 1a, top).[8] The geometrically pure Zn-enolate intermediate could undergo the Mannich reaction to afford synthetically useful α-quaternary β-amino-aldehydes with excellent enantio- and diastereoselectivity. The transition-metal-catalyzed α-allylation is another emerging strategy to construct quaternary carbon centers (Scheme 1a, middle).[9] The groups of List[9b] and Gong[9e] have successfully carried out the reaction by synergistic catalysis using a π-allyl-Pd-TRIP ion pair complex with achiral amine in excellent selectivities. In 2016, the Evans group reported an unprecedented example where an aldehyde, activated by strong base, was able to react with a chiral π-allyl-rhodium intermediate to synthesize enantioenriched α-quaternary aldehydes.[9d] Despite the success for construction of chiral quaternary stereocenters, the established methods to control the enantioselectivity are limited to above two major approaches, thus limiting the types of products. Thus, from the synthetic point of view, the development of mechanistically new strategies to control the enantioselective synthesis of α-quaternary aldehydes is still highly

Scheme 1. The existing asymmetric catalytic strategies for the construction of α-quaternary aldehydes and our new design for construction α-quaternary aldehydes through Pd-catalyzed alkylation reaction.



desirable. In conjunction with our long-standing interest in the π-allyl palladium controlled asymmetric reaction.[10] We envisioned that a neighboring π-allyl palladium motif, installed at the α-position of an aldehyde, might dominate the enantio- and diastereoselective induction for the construction of a quaternary carbon center (Scheme 1a, bottom). In this context, we disclose a novel Pd-catalyzed enantio- and diastereoselective α-quaternary alkylation of α-branched aldehydes to synthesize complex cyclic compounds (Scheme 1b). We devised the bifunctional substrate **1** which incorporated both an allyl carbonate and an α-formyl methine moiety. We proposed that the reaction proceeded through the zwitterionic Pd-complex intermediate **I**, generated *in situ* by the ionization of the allyl carbonate followed by the base-assisted deprotonation. The stereoselective enolization of intermediate **I** would lead to the key intermediate **II**, which then reacted with prochiral π-system coupling partners to deliver the cyclic adducts bearing an α-quaternary carbon center along with one or two additional contiguous stereocenters,

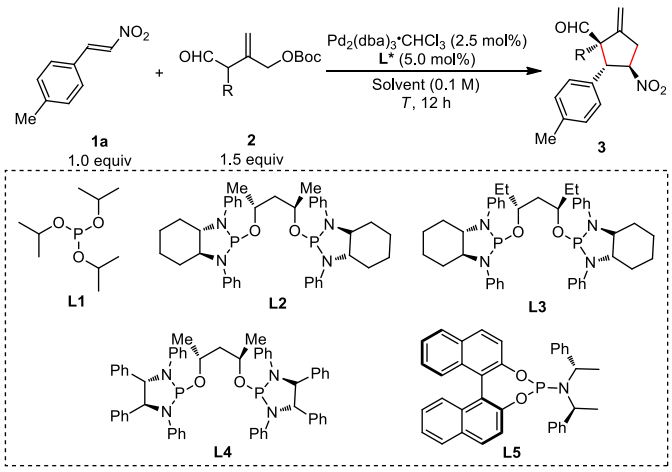
which is the first report of generating such structural elements. From another perspective, we are disclosing a highly diastereo- and enantioselective approach for hetero- and carbocyclic five-membered ring systems analogous to what the Diels-Alder reactions succeeded for the six membered rings, where the high efficiency and selectivities are enabled by the high conformational control of the diene and dienophile.[11] The importance of the Diels-Alder reactions for six membered ring systems foreshadowed the substantial applications of analogous reactions to make five membered rings. However, additional challenges arise from the fact that: 1) unlike direct installing the chiral porckets on the heteroatom of enolate or the electrophiles, whether the neighboring π-allyl palladium motif could give the appropriate asymmetric induction for this transformation, 2) the intermediate **I** is prone to undergo the aldol condensation and other potential undesired pathways,[12] 3) an examination of the structural requirements of this process involving an enolate with no control of the enolate olefin geometry would lead to a prediction of poor stereocontrol.

RESULTS AND DISCUSSION

With the above questions in mind, we first probed the racemic reactions by reacting nitroolefin **1a** with bifunctional allyl carbonate **2a** in the presence of $Pd_2(dba)_3$•$CHCl_3$ and triisopropyl phosphite **L1** in THF at 60 °C (see Table 1). The desired cyclic adduct **3aa** bearing a quaternary carbon center could be isolated in 83% yield, albeit with poor diastereoselectivity (entry 1). With the racemic reaction established, we turned our efforts to realizing the enantioselective transformation by applying chiral phosphorous ligands. A chiral diamidophosphite ligand **L2** showed excellent reactivity and diastereoselectivity with promising enantioselectivity (entry 2). Toluene and 1,4-dioxane did not give better results (entry 3-4). Interestingly, increasing the steric bulk about the ligand backbone led to a distinct improvement in enantioselectivity but with an erosion of

diastereoselectivity (entry 5-6). Use of the phosphoramidite ligand (Feringa ligand) **L5** led to poor reactivity (entry 7). When the reaction was conducted in other solvents at lower temperature, DME was found to be ideal in terms of reactivity and selectivity (entry 8-10). Both the diastereoselectivity and enantioselectivity were slightly increased when the reaction was performed at 35 °C (entry 11). Surprisingly, the reaction was completely shut down at room temperature (entry 12). Extending the methyl group at the α-position of aldehyde to an ethyl group had a beneficial effect on diastereoselectivity, which is presumably conducive to the geometrically more controlled enolization of intermediate **II** (entry 13). Gratifyingly, after briefly screening various solvents, the desired product **3ab** was isolated in 89% yield with excellent diastereoselectivity and enantioselectivity (12:1 *dr* and 99:1 *er*) in the presence of 1,4-dioxane (entry 14-16). Interestingly, the cyclohexane diamidophosphite **L2** also gave excellent results under this reaction condition (entry 17).

Table 1. Optimization of reaction condition



Entry[a]	ligand	R	Solvent	T (°C)	Yield	Er[b]	Dr[c]
1	L1	Me	THF	60	83%	/	2:1
2	L2	Me	THF	60	90%	85.5:14.5	10:1

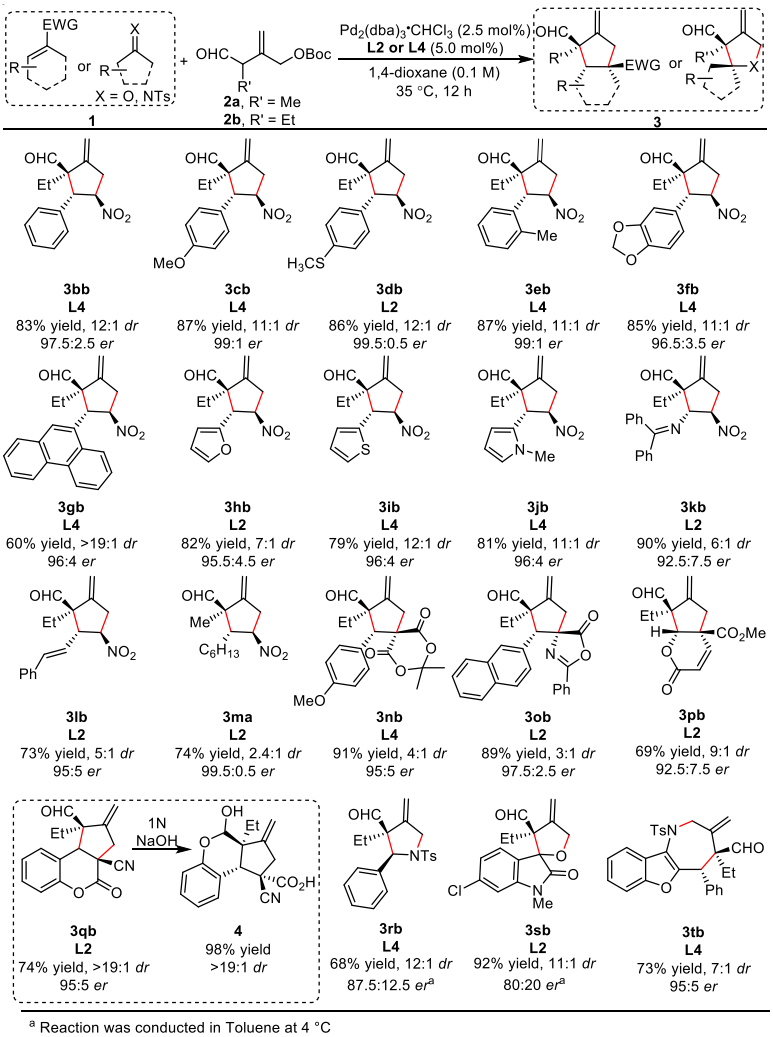
3	L2	Me	Dioxane	60	85%	84.5:15.5	6:1
4	L2	Me	Toluene	60	89%	85:15	7:1
5	L3	Me	THF	60	71%	86:14	8:1
6	L4	Me	THF	60	85%	91.5:8.5	5:1
7	L5	Me	THF	60	21%	/	4:1
8	L4	Me	THF	40	82%	92:8	5:1
9	L4	Me	2-Me-THF	40	86%	92.5:7.5	7:1
10	L4	Me	DME	40	88%	94:6	8:1
11	L4	Me	DME	35	85%	95:5	9:1
12	L4	Me	DME	rt	<10%	/	/
13	L4	Et	DME	35	72%	93:7	13:1
14	L4	Et	THF	35	65%	98.5:1.5	12:1
15	L4	Et	Toluene	35	68%	99:1	14:1
16	L4	Et	Dioxane	35	89%	99:1	12:1
17	L2	Et	Dioxane	35	90%	97:3	13:1

[a]Reactions were performed on a 0.10 mmol scale for 12 h. [b]Enantiomeric ratio (er) determined using chiral HPLC. [c]Diastereomeric ratio (dr) determined by crude ^{1}H NMR.

With the optimized conditions in hand, we proceeded to evaluate the generality of this reaction by screening various kinds of π-system coupling partners (Scheme 2). By reacting with α-branched aldehydes **2a** or **2b**, the nitrostyrenes with various steric and electronic properties behaved very well to afford the desired products with good yield (60-90%), excellent enantioselectivities (up to 99.5:0.5 *er*) and moderate to excellent diastereoselectivities (up to 19:1 *dr*). With respect to the aromatic ring in the nitroolefin, a series of substituents such as methoxy (**1c**), methylthio (**1d**), methyl (**1e**) and methylenedioxy (**1f**) groups at *para*- or *ortho*-positions were well tolerated and gave the anticipated products in excellent results. It is worth noting that, the nitroolefin **1e,** bearing a sterically congested group, proceeded smoothly in the reaction. Moreover, substrates containing

medicinally relevant heteroaromatics (**1h-j**) could also undergo the cycloaddition efficiently with good results. Notably, the nitroolefin is not limited to aromatic substituted ones. Benzophenone imine substituted nitroethylene **1k** and conjugated 1,3-nitrodienes **1l** also proved to be feasible, thus yielding synthetically useful cyclopentane structures. Moreover, a general and representative aliphatic nitroolefin **1m** could also participate in this transformation to give the anticipated product **3ma** with 2.4:1 *dr* and 99.5:0.5 *er*. To our surprise, the nitrostyrenes with electron-withdrawing groups (4-chloro or 4-CF_3) on the phenyl ring did not give the desired products at all.[13]

Scheme 2. Scope with respect to π-system coupling partners

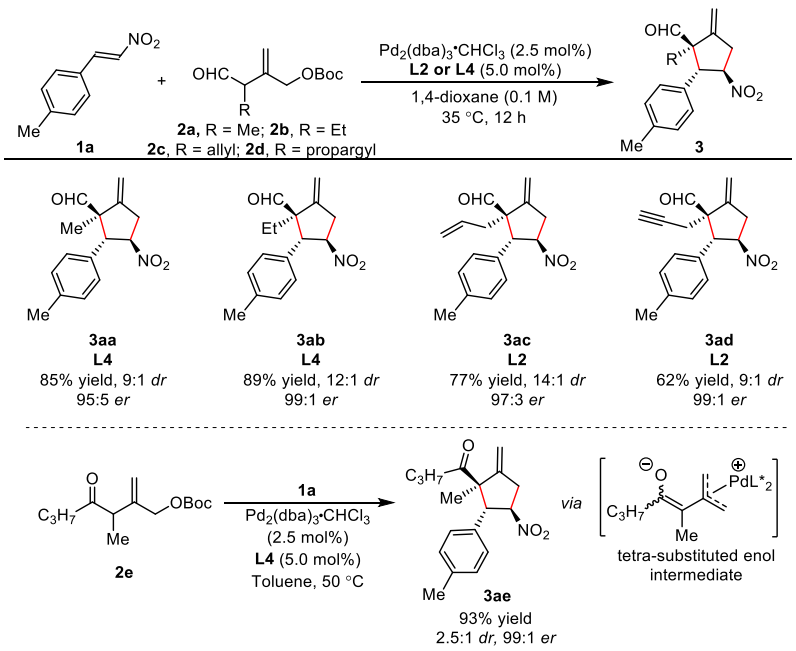


[a] Reaction was conducted in Toluene at 4 °C

The coupling partners of this reaction are not limited to nitroolefins. Other types of electron-deficient π-systems such as Meldrum's acid alkylidene **1n**, azlactone **1o**, pyrone **1p** and coumarin **1q** were demonstrated to be applicable and gave the corresponding cyclic adducts in 69-91% yields and excellent diastereo- and enantioselectivities (up to 19:1 *dr* and 97.5:2.5 er). Upon treating **3qb** with 1N NaOH under mild condition, the highly functionalized cyclopentane carboxylic acid **4** could be obtained in quantitative yield. Ts-imine **1r** served as an excellent partner in this reaction thereby extending the method to access biologically important substituted pyrrolidines. The absolute configuration was assigned by comparison to optical rotation of known compound **3rb**.[14] Notably, tetrahydrofuran bearing two vicinal tetra-substituted stereogenic centers, which would be challenging to synthesize by conventional chemical strategies, could be easily accessed in good diseteroselectivity and promising enantioselectivity. Much to our delight, the azadiene **1t** prefered the [4+3] type cycloaddition pathway,[15] leading to the entropically disfavored medium-sized benzofuro[3,2-*b*]azepines with a quaternary carbon center in excellent result.

To further expand the generality of this process, α-branched aldehydes with other substituents were subjected to the reaction (Scheme 3). Attaching an alkene functionality to the methyl chain proceeded without an erosion of stereoselectivity or reactivity. To our surprise, the terminal alkyne group was tolerated in this transformation and led to synthetically important 1,5-enyne unit[16] with excellent enantioselectivity and moderate diastereoselectivity. Delightfully, the preliminary result showed that α-branched ketone **2e** was also an effective in this transformation and gave the corresponding α-quaternary ketone adduct **3ae** in excellent yield and enantioselectivity, albeit with diminished, but synthetically useful diastereoselectivity.

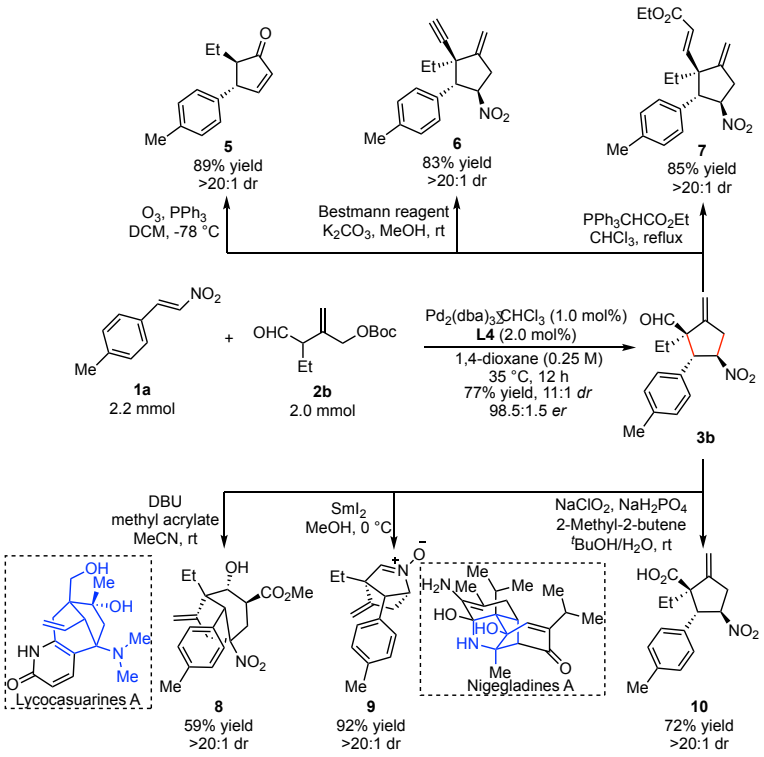
Scheme 3. Scope with respect to α-branched aldehydes and preliminary result for α-branched ketone



To showcase the synthetic potential of our protocol for scaled applications, the millimole reaction was conducted with reduced loadings of the catalyst and the ligand by increasing the reaction concentration to 0.25 M. The levels of diastereomeric and enantiomeric enrichment at 1.0 mol % of $Pd_2(dba)_3$•$CHCl_3$ remained unchanged (Scheme 4, middle). In order to demonstrate the utility of our method for generating interesting and useful chiral building blocks, a number of selective transformations were carried out. Ozonolysis of **3ab** smoothly provided the cyclopentenenone **5,** formed through the elimination of HNO_2 and decarboxylation. Seyferth-Gilbert homologation of the aldehyde furnished alkyne **6** efficiently in 83% yield.[17] The adduct **3ab** could also be applied to the Wittig reaction to give chiral 1,4-diene **7**. To our surprise, the structurally complex bridged ring systems **8** could be accessed through the base-assisted Michael addition and intramolecular aldol reaction. In addition, the bicyclo[2.2.1] nitrone **9** could be obtained in near quantitative yield upon treating **3ab** in the reducing condition.[18] Pinnick oxidation of aldehyde **3ab** provides an efficient route to the α-quaternary carboxylic acid **10** with good yield.[19] It should be notable that

these transformations open an efficient and unique avenue to access polyfunctionalized cycloadducts, which are difficult or even impossible to obtain by other strategies.

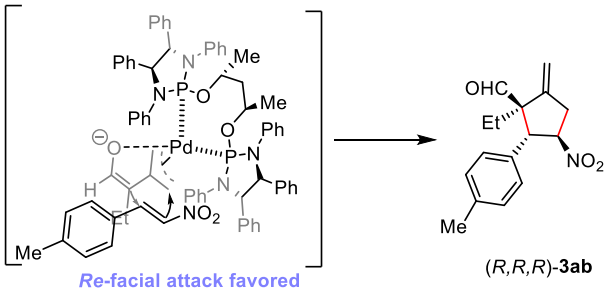
Scheme 4. Large-scale preparation of **3ab** and its derivatization



The stereochemical outcome of this transformation can be rationalized by consideration of the geometry of the π-allyl palladium/enolate intermediate (Scheme 5). A *cis* relationship between the enolate oxygen and the π-allyl is likely a result of either two-fold binding to palladium or electrostatic interactions between the charged moieties of the zwitterionic intermediate. Additionally, this orientation may minimize ligand interactions with the alkyl side chain and potentially explains the increase in diastereoselectivity when changing the side chain from a methyl to ethyl substituent. The extension of chiral information in the ligand allows for translation to the site of the conjugate addition, favoring addition to the *Re* face with the bulky aromatic substituent of the π-acceptor aligned away from the palladium complex. The seeming stereospecificity in product formation with respect to the substituents on the acceptor gives some

credence to the idea that the reaction is a concerted cycloaddition; however, the thermodynamic *trans* relationship could simply be favored in a step-wise mechanism.

Scheme 5. Plausible stereochemical mode of **3ab**



CONCLUSIONS

In summary, we have disclosed an unprecedented strategy to control the enantioselective alkylation of α-branched aldehydes to synthesize chiral cyclic α-quaternary aldehydes with one or two additional contiguous stereocenters. In contrast to the previous strategies, this new strategy does not rely on the use of external chiral amine, base or chiral electrophiles to construct the α-quaternary aldehydes, but instead relies on a chiral palladium complex for stereoinduction. Impressively, the diastereo- and enantioselective event occurs as a Michael addition distal to the chiral information. This is further emphasized since the *in-situ* generated π-allyl-Pd species on the carbon center of enolate has been validated to undergo the chiral induction efficiently in the construction of quaternary carbon center. An array of synthetically useful and flexible hetero- and carbocycles were efficiently assembled. Furthermore, elaborations of the available multifunctional cycloadducts enabled rapid access to a wide range of structural types, which are ubiquitous in complex molecular targets. Due to its convergency, this reaction exemplifies themes of step and atom economy.[20] Furthermore, the ease of post-synthetic modifications by selective functional

group interconversions renders this reaction practical for diversity-oriented synthesis, an increasingly important strategy in drug discovery.[21]

ASSOCIATED CONTENT

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡Z. Z. and Y. W. contributed equally.

Notes

The authors declare no competing financial interest.

Supporting Information.

Complete experimental procedures, compound characterization, representative NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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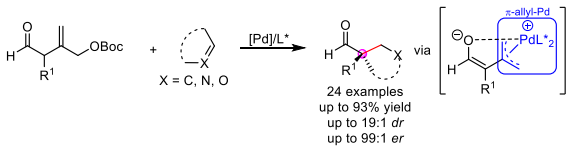
Table of Content

Pd(0)-catalyzed Chemo-, Diastereo- and Enantioselective α-Quaternary Alkylation of Branched Aldehydes



Quaternary carbon stereocenters are ubiquitous in a wide variety of organic compounds and drug molecules. A novel strategy to control the enantioselective construction of chiral α-quaternary aldehydes from racemic α-branched aldehydes was achieved. The synthetic utility of the products has been highlighted by a series of derivatizations and the potential of this method extended to the synthesis of chiral α-quaternary ketones.