Enantioselective Tertiary Electrophile (Hetero)Benzylation: Pd-Catalyzed Substitution of Isoprene Monoxide with Arylacetates

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Abstract The enantioselective generation of quaternary carbon centers remains challenging but is of growing importance for the preparation of functional molecules. Transition metal catalyzed allylic alkylations of tertiary electrophiles have provided access to these substructures but remain generally incompatible with organometallic benzyl nucleophiles. In this study we demonstrate that electron-deficient arylacetates can serve as benzyl nucleophile surrogates to generate enantioenriched acyclic molecules containing a quaternary carbon center via a two-step substitution-decarboxylation process using isoprene monoxide. The reaction gives products typically in >90% ee using a commercially available catalyst system and tolerates an array of electron-withdrawing functional groups on the arylacetate moiety. The lactone intermediate generated by the initial substitution reaction can be used in further stereoselective transformations to prepare molecules with acyclic vicinal quaternary stereocenters.

Stereogenic quaternary carbon centers are found in many bioactive molecules and pharmaceuticals.[1] It is becoming more common that clinical candidates feature these units as medicinal chemistry programs seek out targets with increased three-dimensional structure.[2] The catalytic, enantioselective preparation of acyclic quaternary carbon centers is made difficult by the steric encumbrance of substrates, the potential for poor orbital overlap between reactants, and the necessity for catalysts to differentiate between three non-hydrogen groups in molecules with high conformational freedom. Despite these challenges, the field of enantioselective synthesis of acyclic molecules bearing quaternary carbon centers has flourished thanks to an increased understanding of reaction mechanisms, new families of chiral catalysts, and improved tactics to generate reactive intermediates under mild conditions.[3]

Current state-of-the-art methods for the preparation of stereogenic quaternary carbon units include transition metal catalyzed allylic substitutions.[4] Despite rapid advances in the areas of metal-catalyzed allylic alkylations using both hard[3e, 5] and soft[6], [7] carbon nucleophiles, certain structural classes of quaternary carbon units remain inaccessible by these approaches. Currently, the direct enantioselective benzylation of tertiary allylic electrophiles with main-group organometallics remains

unknown.[8] In this regard, it would be desirable to develop new approaches to enantioselective allylic benzylations where surrogates for hard C(sp^3)-nucleophiles are used. Alternative strategies for the enantioselective (hetero)benzylation of secondary allylic electrophiles include the use of deprotonated Lewis acid stabilized methyl azaheterocycles in combination with a strong base,[9] benzylic deprotonation of $Cr(CO)_3$ activated toluenes followed by decomplexation,[10] fragmentation of 4-benzyl-dihydropyridines with photoredox co-catalysts,[11] and the use of electron-rich diene nucleophiles that can undergo aromatization upon allylation (Fig 1a).[12] A recent report established 4-benzyl-dihydropyridines can be used to generate quaternary benzylated stereocenters using α-aryl allylic carbonate electrophiles; however enantioselectivities remain modest (generally ~80% ee).[13] We previously developed a decarboxylative approach towards the enantioselective benzylation of secondary allylic electrophiles using arylacetic acids as pronucleophiles.[14] In these reactions, decarboxylation occurs after stereoselective allylation. We questioned whether this concept could be expanded for the benzylation of tertiary allylic electrophiles, focusing on isoprene monoxide as it is an archetypal electrophile and is widely used in complex molecule synthesis.[15] Here we report that Trost-type chiral Pd catalysts facilitate the enantioselective allylic alkylation of (hetero)arylacetate esters to generate lactone intermediates (Fig 1b). Subsequent hydrolysis and decarboxylation of the lactone generates acyclic products with chiral benzylated quaternary stereocenters, typically in >90% ee. The ester group of the arylacetate acts as a traceless modifying group to tune reactivity. In addition, the lactone intermediates can be converted into acyclic products with vicinal quaternary stereocenters in a stereodivergent manner by an allylation-reductive ring-opening sequence (Fig 1b).

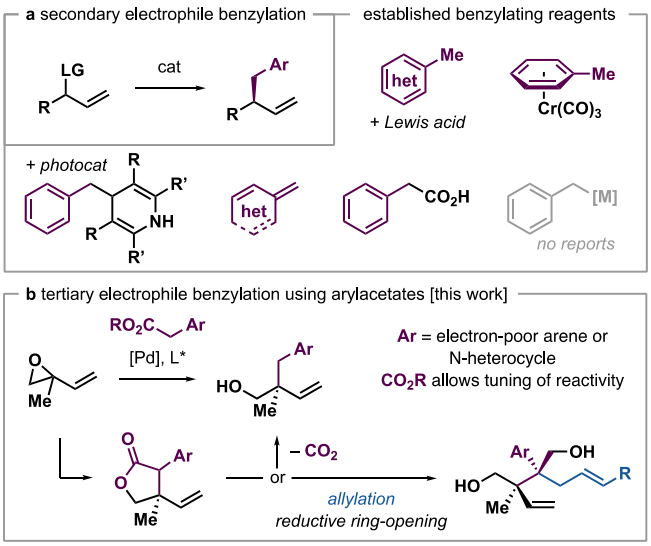
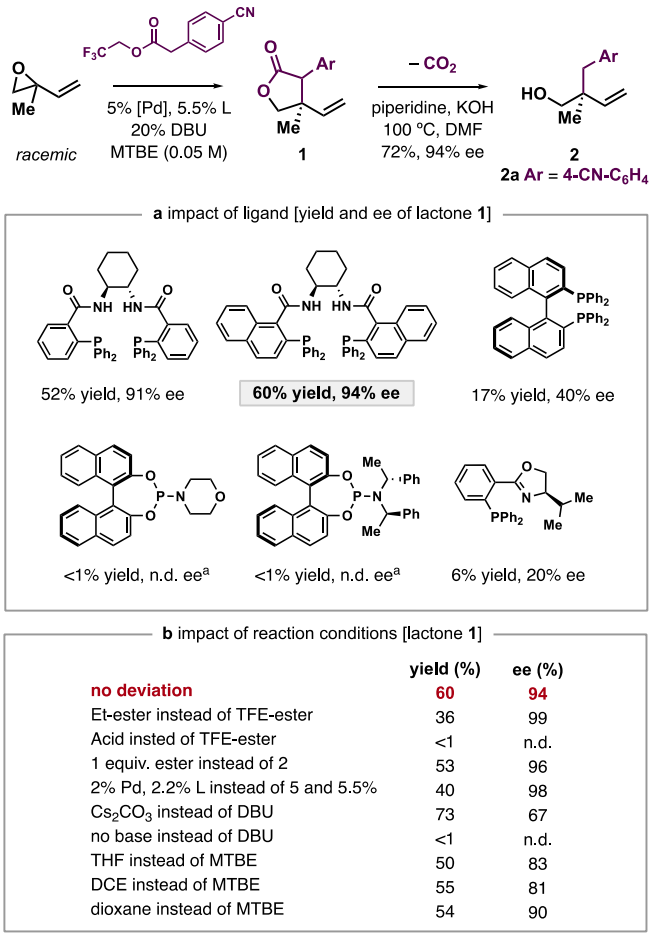


Figure 1. [a] Overview of approaches for allylic alkylation using benzylic nucleophiles with secondary electrophiles, [b] this study showing an arylacetate surrogate approach for the benzylation of isoprene monoxide.

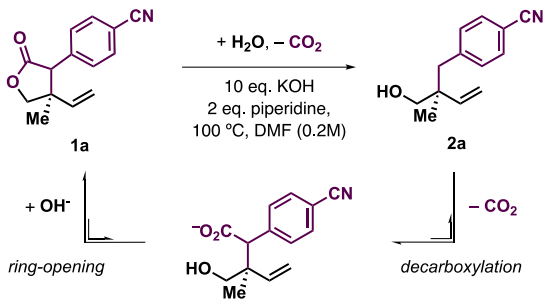
Reaction conditions and benzylic nucleophile surrogates were broadly examined with the aim of promoting enantioselective tertiary electrophile benzylation. It was ultimately found that the combination of 2.5 mol% $[Pd(cinnamyl)Cl]_2$ and 5.5 mol% Nap-Trost ligand catalyzes the enantioselective addition of the 2,2,2-trifluoroethyl (TFE) ester of 4-cyanophenylacetate to isoprene monoxide to generate lactone **1** in 60% yield and 94% ee (Fig 2). Lactone **1** is formed as an inconsequential ~2:1 mixture of diastereomers and undergoes thermal decarboxylation to give the benzylated quaternary stereocenter containing product **2** in 72% isolated yield without the erosion of product ee (94%). Other ligand classes, including bisphosphines, phosphoramidites, and Phox ligands were inferior to Trost-type ligands (Fig 2a). The corresponding ethyl ester of 4-cyanophenylacetate, which reacted at a slower rate, led to formation of **1a** in 36% yield and 99% ee. Reducing the equivalents of the TFE-ester from two to one or reducing the catalyst loading from 5 mol% to 2 mol% also slowed reaction rates and gave lower terminal yields but slightly increased enantioselectivities compared to the standard conditions (Fig 2b, 53% yield, 96% ee and 40% yield, 98% ee respectively). The use of Cs_2CO_3 instead of DBU as the base led to faster reactions with smooth conversion to product, but at the expense of enantioselectivity (73% yield, 67% ee). In general, conversion of isoprene monoxide was >95%; with the remaining mass balance comprising of non-productive consumption of the epoxide (1,4-linear addition, diene and aldehyde formation, lactone allylation). These optimization studies highlight that reaction enantioselectivity is inversely related to rate, likely because the intermediate Pd-allyl species requires time to undergo η^3-η^1-η^3 isomerization to interconvert between allyl diastereomers.[16] Unfortunately, decreased reaction rates also lead to an increased amount of side product formation due to non-productive consumption of the epoxide. The optimized conditions therefore provide a compromise between selectivity and yield; however, in cases where ≥98% product ee is desirable, greater enantioselectivity can be achieved under modified conditions (Fig 2b).



	yield (%)	ee (%)
no deviation	**60**	**94**
Et-ester instead of TFE-ester	36	99
Acid insted of TFE-ester	<1	n.d.
1 equiv. ester instead of 2	53	96
2% Pd, 2.2% L instead of 5 and 5.5%	40	98
Cs_2CO_3 instead of DBU	73	67
no base instead of DBU	<1	n.d.
THF instead of MTBE	50	83
DCE instead of MTBE	55	81
dioxane instead of MTBE	54	90

Figure 2. Optimization studies for the Pd-catalyzed enantioselective benzylation of racemic isoprene monoxide. Vinyl epoxide:arylacetate = 1:2. [a] Impact of ligand, [b] impact of reaction conditions. Yields determined by calibrated ^{1}H NMR, ee determined by chiral HPLC, lactone dr = 66:34, reaction time 7–18 h at room temperature. [Pd] = $[Pd(cinnamyl)Cl]_2$, [a]11 mol% ligand used.

At the outset of this study, it was not immediately certain whether lactone **1** would undergo decarboxylation in high yield. Generation of **2** requires ring-opening lactone hydrolysis and decarboxylation;[17] both steps are reversible and decarboxylation is suppressed by water (Fig 3).[18] It was found that the use of a polar aprotic solvent (DMF) at 100 ºC with an excess of KOH and piperidine provided optimal results (Fig 3, 78% yield of **2a**, complete retention of stereochemistry). The piperidine likely acts as a Lewis base to capture the liberated CO_2, which stymies re-carboxylation of the anionic benzyl intermediate.[18]



variation to standard conditions

	conv (%)	yield (%)
none	92	78
no piperdine	88	63
TBME instead of DMF	>99	<1
DMSO instead of DMF	82	<1
10% by volume H_2O	51	37
2 equiv KOH	63	49
80 °C instead of 100 °C	79	63

Figure 3. Effect of reaction parameters on lactone ring-opening decarboxylation. Yields determined by calibrated ^{1}H NMR, reaction time 40–48 h.

The net enantioselective decarboxylative benzylation of isoprene monoxide accommodates an array of electron-poor (hetero)arylacetates to give products **2** in 85–99% ee (Fig 4a). Benzylated products containing aryl cyano, nitro, carbonyl, sulfonyl, sulfonamide, trifluoromethyl, chloro, and pentafluorosulfanyl groups are tolerated (**2a**–**2j**). For arylacetates that are more electron-deficient than 4-cyanoarylacetate, the use of the corresponding ethyl ester in THF with Cs_2CO_3 as the base was found to give higher enantioselectivities (**2b**, **2d**, and **2o**, see SI for a comparison of conditions). The use of the ethyl ester of these substrates decreases the acidity of the substrate in comparison to the TFE-ester, which in turn decreases the concentration of the reactive enolate nucleophile in solution and allows for a slower reaction that proceeds with higher enantioselectivity. Chiral products featuring electron-poor N-heterocycles, including 2- and 4-pyridines, 2-pyrazine, and 2-quinoline (**2k**–**2o**) can be generated smoothly in good ee. While products with electron-neutral or electron-rich arenes are not directly amenable to the reaction (see the SI for unsuccessful substrates), these benzylated fragments can be easily obtained by, for example, reduction of the nitro group in **2b** to generate aniline **2p**. Subsequent deamination gives benzyl product **2q**.

The lactone intermediate from the first step does not require rigorous purification prior to decarboxylation. Filtration through a silica plug to remove base and the bulk of catalyst, followed by a solvent swap leads to similar overall two-step yields (see the SI for more details). The lactonization/decarboxylation approach provides access to benzylated products that are not accessible by known approaches. For example, direct benzylation of isoprene monoxide to prepare **2r** with benzyl magnesium bromide or benzyl zinc reagents leads only to racemic products in modest yields. The use of Lewis acid complexation/deprotonation approaches for heterobenzylations that are viable for

secondary electrophiles also fail when using tertiary epoxide electrophiles, for example to prepare **2j** (Fig 4b).[30]

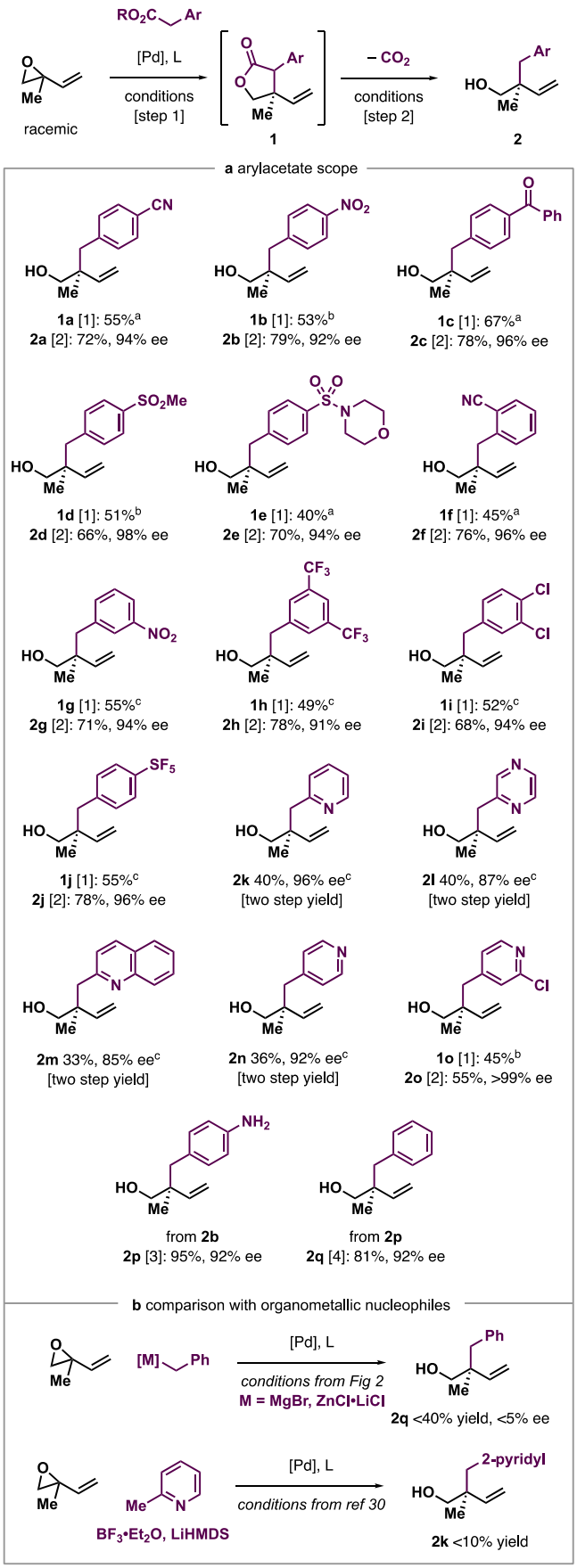

RO2C Ar
[Pd], L
conditions
[step 1]
racemic
1
– CO2
conditions
[step 2]
2
a arylacetate scope
1a [1]: 55%a
2a [2]: 72%, 94% ee
1b [1]: 53%b
2b [2]: 79%, 92% ee
1c [1]: 67%a
2c [2]: 78%, 96% ee
1d [1]: 51%b
2d [2]: 66%, 98% ee
1e [1]: 40%a
2e [2]: 70%, 94% ee
1f [1]: 45%a
2f [2]: 76%, 96% ee
1g [1]: 55%c
2g [2]: 71%, 94% ee
1h [1]: 49%c
2h [2]: 78%, 91% ee
1i [1]: 52%c
2i [2]: 68%, 94% ee
1j [1]: 55%c
2j [2]: 78%, 96% ee
2k 40%, 96% eec
[two step yield]
2l 40%, 87% eec
[two step yield]
2m 33%, 85% eec
[two step yield]
2n 36%, 92% eec
[two step yield]
1o [1]: 45%b
2o [2]: 55%, >99% ee
from 2b
2p [3]: 95%, 92% ee
from 2p
2q [4]: 81%, 92% ee
b comparison with organometallic nucleophiles
[M] Ph
[Pd], L
conditions from Fig 2
M = MgBr, ZnCl•LiCl
2q <40% yield, <5% ee
BF3•Et2O, LiHMDS
[Pd], L
conditions from ref 30
2k <10% yield

Figure 4. Scope of the Pd-catalyzed benzylation of isoprene monoxide. [a] Arylacetate nucleophile scope, [b] comparison with organometallic nucleophiles. [Pd] = $[Pd(cinnamyl)Cl]_2$, L = (*R,R*)-Nap-Trost. Ring opening decarboxylation temperature 95 – 130 ºC in DMF. Step [3] nitro reduction, step [4] deamination, see SI for complete details. Yields are of isolated material unless otherwise noted. [a]From TFE-ester using 20 mol% DBU in MTBE. [b]From Et-ester using 60 mol% Cs_2CO_3 in THF. [c]From TFE-ester using 40% DABCO in MTBE.

In lieu of decarboxylation, the lactone generated by arylacetate substitution of isoprene monoxide can serve as an intermediate for other stereoselective transformations to generate different classes of acyclic molecules bearing quaternary carbons. Pd-catalyzed lactone allylation[19] followed by $LiBH_4$ mediated reductive ring-opening[20] of **1a** leads to diol products **4** that feature vicinal quaternary stereocenters in yields of 62–74% over two steps (Fig 5).[6a, 21] Access to either product diastereomer is possible by stereodivergent lactone allylation.[22] When using (*R,R*)-Nap-Trost in the benzylation of isoprene monoxide, the use of the (*S,S*) series of Trost-ligands in the subsequent lactone allylation leads to diol products in ≥97% ee and ≥94:6 dr (**4a**, **4b**). The use of the (*R,R*) series of Trost-ligands leads to the opposite diastereomer in ≥99% ee and ≥66:34 dr (**4a'**, **4b'**).

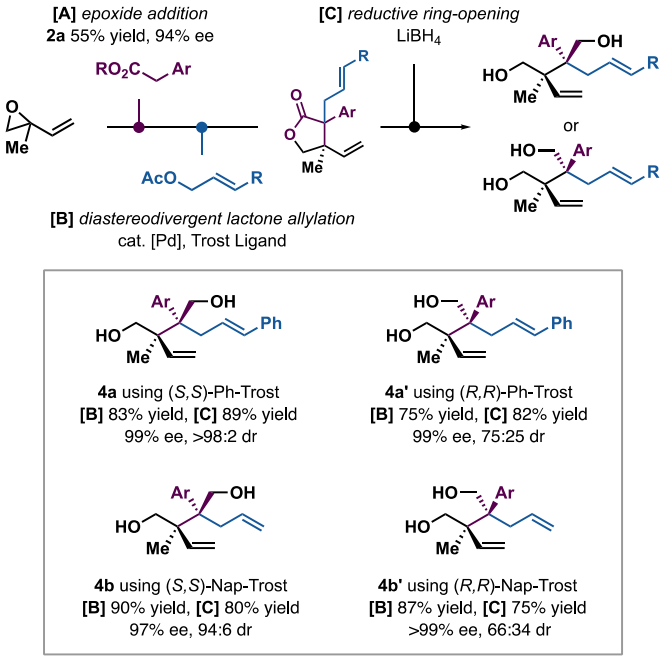


Figure 5. Diastereodivergent synthesis of targets with vicinal acyclic quaternary stereocenters by lactone allylation and reductive ring-opening.

Transition metal-catalyzed allylic alkylations are among the most robust methods to generate enantioenriched acyclic quaternary stereocenters. This work demonstrates that easy to prepare, bench stable arylacetates can act as surrogates for highly basic organometallic benzylic nucleophiles in allylic

substitution reactions of tertiary electrophiles. After ring-opening decarboxylation of the lactone intermediates, (hetero)benzylated products can be obtained in generally >90% ee. The lactone can also serve as an intermediate in the synthesis of additional classes of chiral acyclic allylated products *via* catalyst-controlled diastereodivergent reactions. This approach may find value in other classes of enantioselective reactions that are incompatible with classical organometallic benzylating reagents.

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Conflict of Interest

The authors declare no conflict of interest.

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