CHAPTER 1

Expanding Insight into the Asymmetric Palladium-Catalyzed Allylic Alkylation of N-Heterocyclic Molecules and Cyclic Ketones[†]

1.1 INTRODUCTION AND BACKGROUND

The asymmetric construction of quaternary stereocenters is a topic of great interest in the organic chemistry community. Among the available methods that afford this motif,[1] palladium-catalyzed decarboxylative allylic alkylation[2,3] has proven particularly effective and, over the last decade, our group has pursued this strategy employing chiral phosphinooxazoline (PHOX) ligands.[4,5] Our initial efforts in this area led to the preparation of enantioenriched α-quaternary ketones (e.g., **2a**) in good yields and enantioselectivities using (*S*)-*t*-BuPHOX (**3**)[5a–b] as a chiral ligand (Scheme 1.1A).[6] Since these early results, we have considerably expanded the scope,[7] demonstrated multiple applications,[8] and performed mechanistic investigations[9] of this powerful

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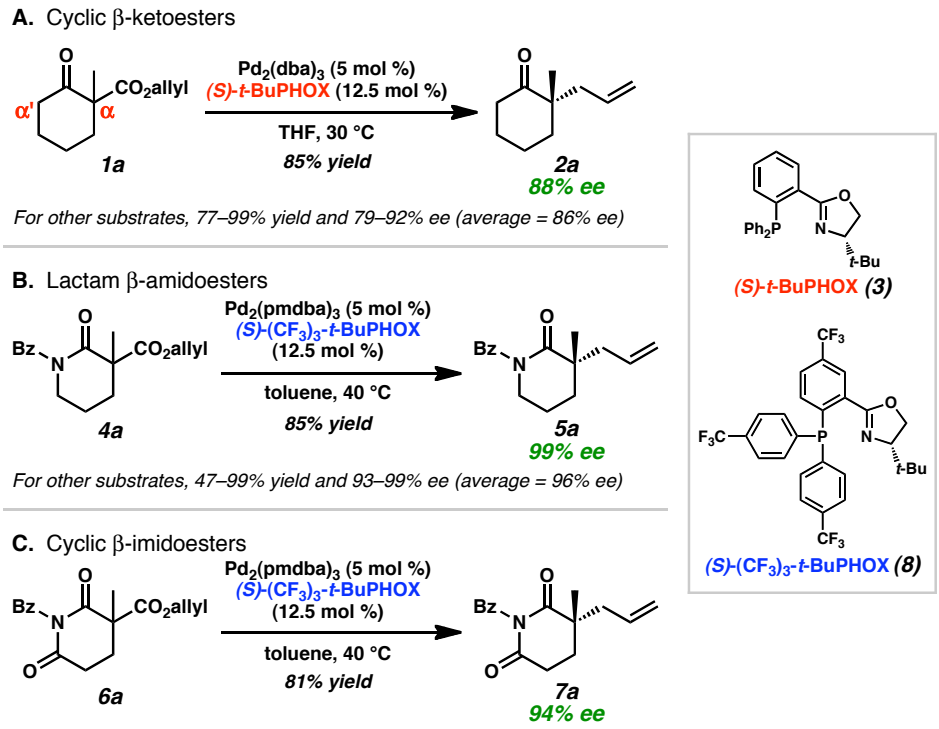
[†] This research was performed in collaboration with Douglas C. Duquette and Drs. Jimin Kim, Wen-Bo Liu, Alexander N. Marziale, Douglas C. Behenna, Scott C. Virgil and has been published. See: Bennett, N. B.[‡]; Duquette, D. C.[‡]; Kim, J.; Liu, W.-B.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem.—Eur. J.* **2013**, *19*, 4414–4418. [‡]N.B.B. and D.C.D contributed equally to this article.

transformation. Recently, we discovered that the allylic alkylation of lactams (**4a** to **5a**) and imides (**6a** to **7a**) with (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**)[5c] consistently proceeds with enantioselectivities substantially higher than any other substrate class previously examined in this system (Scheme 1.1B and C).[10] This observation prompted us to investigate which characteristics distinguish these molecules as superior alkylation substrates. The basic distinctions between these ketone and *N*-heterocyclic molecules are the deviation in electronic nature of the enolate and the identity of the α'-functionality (i.e., the group flanking the carbonyl at the site opposite of alkylation). Thus, we have designed several new alkylation substrates to examine the relative contribution of each effect. We have found that the exceptional enantioselectivities observed in the lactam/imide series are likely not a result of a purely electronic effect, but a combination of stereoelectronic and steric factors associated with the α'-substituent. To provide a more complete perspective on allylic alkylation selectivity, this chapter also discusses related research efforts performed by other groups.

Scheme 1.1. Comparison of allylic alkylation of ketones, lactams, and imides.

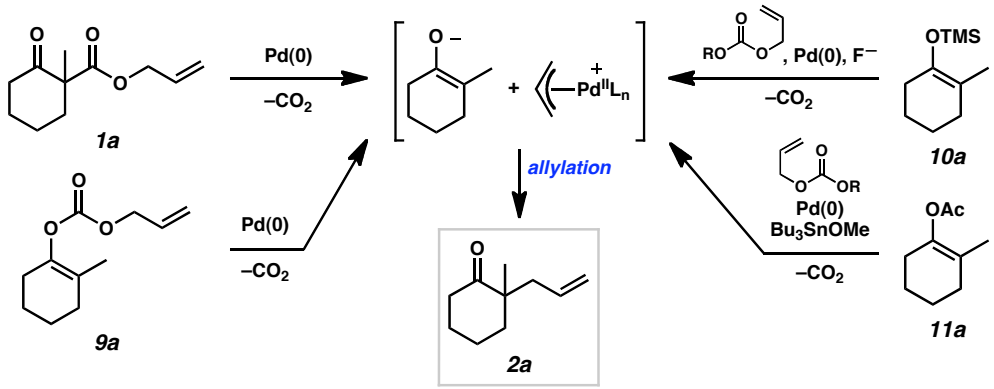


1.1.1 Pd-Catalyzed Asymmetric Allylic Alkylation Background

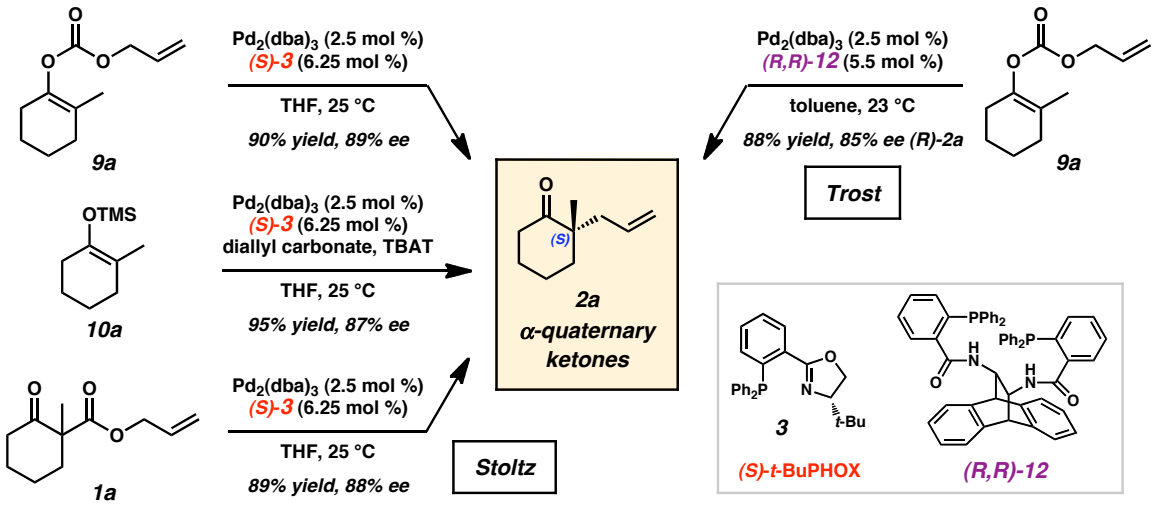
Our entry into asymmetric allylic alkylation methodology began in 2004, when we reported the preparation of α-quaternary cyclic ketones from allyl enol carbonates (**9**) and silyl enol ethers (**10**).[6a] Twenty years prior, Tsuji performed the regioselective allylation of these and other unstabilized enolate precursors under essentially neutral conditions with Pd(0) catalysts (Scheme 1.2).[11] Inspired by Tsuji's approach, we screened a series of chiral *P*,*P*-, *P*,*O*-, and *P*,*N*-ligands in the allylic alkylation of allyl enol carbonate **9a** with $Pd_2(dba)_3$ as a Pd(0) source. Gratifyingly, *P*,*N*-ligands generate the desired enantioenriched ketone product in good yield and ee, with (*S*)-*t*-BuPHOX (**3**) providing the greatest enhancement in selectivity (Scheme 1.3). Silyl enol ethers (**10**)

necessitate the addition of a fluoride source and allyl carbonate, but provide similar results.[6a] We later found that racemic β-ketoesters (**1**) are also excellent substrates under the standard enol carbonate conditions. Notably, β-ketoesters are easy to prepare, are often more stable than the corresponding allyl enol carbonates, and avoid regioselectivity issues in enolate formation with α,β-unsaturated substrates. Following our initial publication, Trost disclosed allylic alkylation conditions for allyl enol carbonates with their C_2-symmetric *P*,*P*-ligands (e.g., (*R*,*R*)-**12**, Scheme 1.3).[2a,12] These initial publications by Stoltz and Trost represent the first examples of the regioselective and enantioselective alkylation of ketones with multiple acidic sites. Although not discussed in this chapter, Hayashi,[13] Ito,[14] Trost,[2a,15] and Hou and Dai[16] have also performed asymmetric alkylation of ketones, however, their approaches require the substrate to possess an occluded α'-position (i.e., one deprotonation site) or a stabilizing α-group (i.e., favored deprotonation site).

Scheme 1.2. Various enolate precursors investigated in the Tsuji reaction.

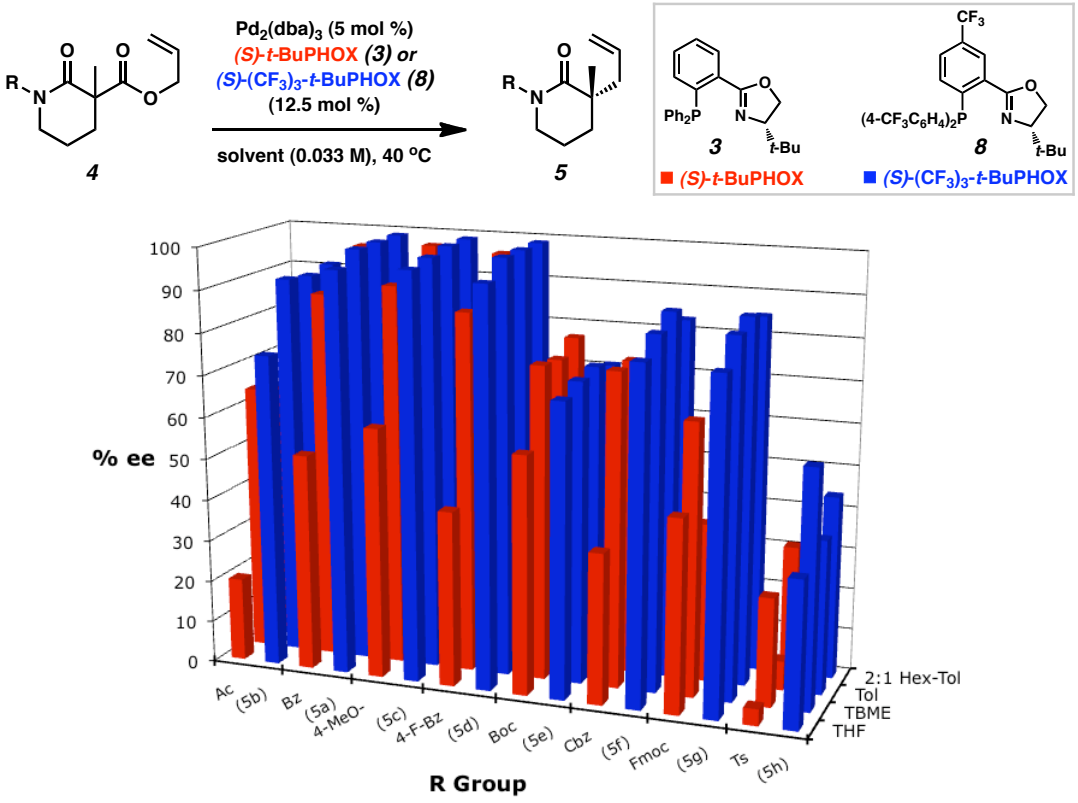


Scheme 1.3. Pd-catalyzed asymmetric allylic alkylations performed by Stoltz and Trost.



As part of our efforts to expand the reaction scope, we explored nitrogen-containing substrates including lactams.[10] Early efforts indicated the *N*-substituent plays a significant role in conversion and enantioselectivity. Notably, electron-rich lactams (*N*-group = Me or Bn) exhibit little to no conversion to the desired products and, as such, are poor alkylation substrates. We consequently prepared a variety of lactams with electron-withdrawing functionality (**4a**–**h**) and screened these molecules against two electronically differentiated chiral ligands, (*S*)-**3** and (*S*)-**8**, and four solvents of varying polarity: tetrahydrofuran (THF), *tert*-butyl methyl ether (TBME), toluene, and 2:1 hexane–toluene (Table 1.1). In general, higher enantioselectivities are observed in less polar solvents with (*S*)-**8** as a ligand. Among the *N*-substituent, benzoyl is optimal and provides nearly perfect selectivity. The transformation is also tolerant of various α-groups and ring sizes and additionally provides high ee for cyclic imides. By comparison, α-quaternary ketones are formed with approximately 10% lower ee, prompting us to question what characteristics distinguish lactams and imides as better substrates.

Table 1.1. Lactam allylic alkylation screen.[a]



					Enantiomeric Excess (% ee)[b]			
entry	substrate *4*	R	product *5*	ligand	THF	TBME	Toluene	2:1 Hex–Tol
1 2	*4b*	Ac	*5b*	*3* *8*	20 75	64 91[d]	62 90[d]	83 91[d]
3 4	*4a*	Bz	*5a*	*3* *8*	52 96	88 99	86 99	96 99
5 6	*4c*	4-MeO-Bz	*5c*	*3* *8*	60 97	91 98	87 99	97 99
7 8	*4d*	4-F-Bz	*5d*	*3* *8*	42 95	86 99	83 99	96 99
9 10	*4e*	Boc[c]	*5e*	*3* *8*	57 70	75 72	74 73	77 71
11 12	*4f*	Cbz	*5f*	*3* *8*	36 80	75 84	75 87	72 83
13 14	*4g*	Fmoc	*5g*	*3* *8*	46 79	65 85	38 87	45 85
15 16	*4h*	Ts[c]	*5h*	*3* *8*	4 35	26 57	7 37	31 44

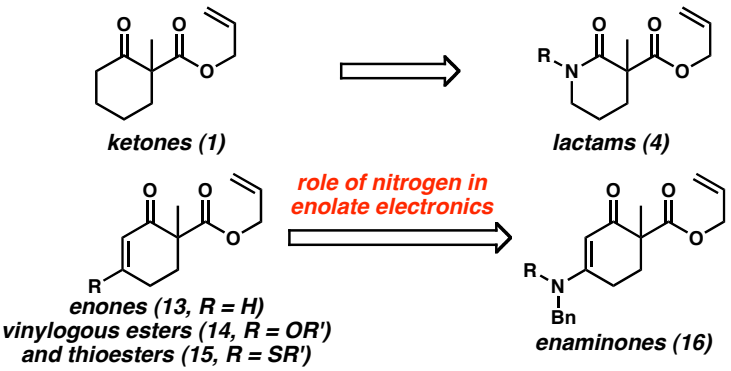
[a] *Conditions*: lactam **4** (1.0 equiv), $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in solvent (0.033 M) at 40 °C. [b] Determined by GC, HPLC, or SFC analysis. Red = with *(S)*-(**3**) as ligand and blue = with *(S)*-(**8**) as ligand. [c] Reaction performed with $Pd_2(pmdba)_3$ at 50 °C. [d] Reaction performed at 60 °C.

1.2 RESULTS AND DISCUSSION

1.2.1 Electronically Variable Substrates

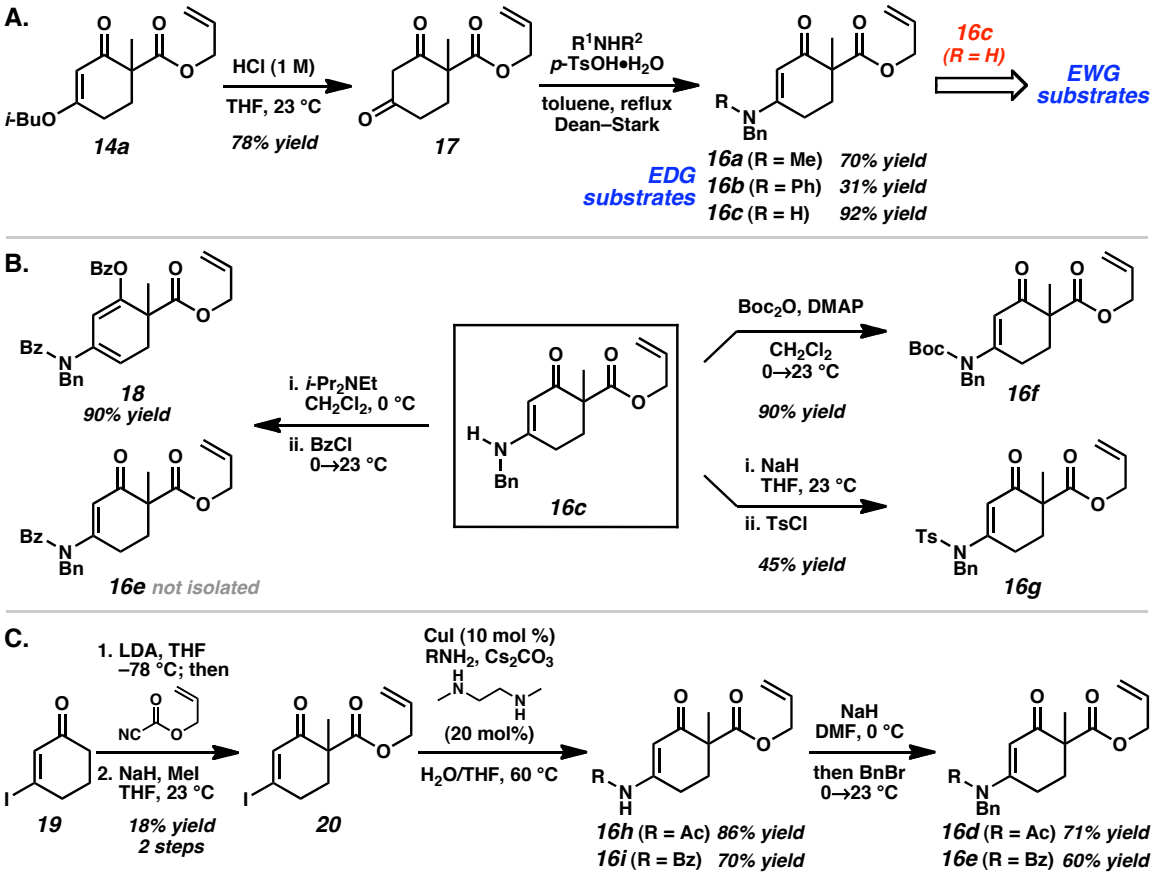
Initially, we hypothesized that the divergence in enolate electronics between the substrate classes depicted in Scheme 1.1 could be the major determining factor of the observed enantioselectivities. Insight from our previous work[9,10] suggested that selectivity in the alkylation of electron-poor and -rich molecules could be considerably different. To investigate the electronic effect of the nitrogen atom on alkylation selectivity without the influence of α'-functionality, we examined variably functionalized enaminones (**16**, i.e., vinylogous amides)[17] as electronic analogues of lactams (**4**, Figure 1.1). We were particularly drawn to this new class of compounds as our past experience with vinylogous esters (**14**)[18] and thioesters (**15**)[18b,19] would provide a foundation and comparison point.[20]

Figure 1.1. Ketone and lactam enantioselectivity divergence as inspiration for investigation of enolate electronics using vinylogous systems.



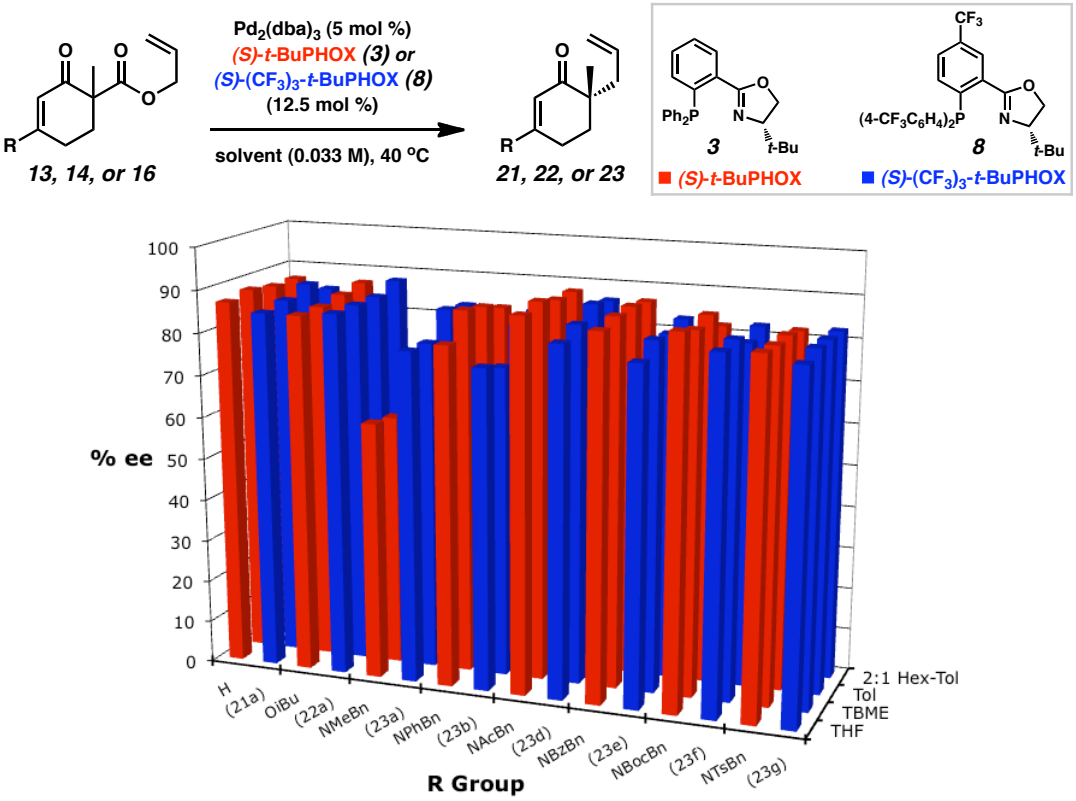
To this end, we prepared a number of racemic enaminone alkylation precursors from vinylogous ester **14a** (Scheme 1.4A). Treatment of vinylogous ester **14a** with hydrochloric acid in THF selectively removes the vinylogous group without hydrolyzing the carboxylic ester, as reported by Desmaële.[21] The resulting dione (**17**) can be condensed with an amine under dehydrative conditions to generate enaminones **16a–c**, which bear electron-donating groups.[22,23,24] To prepare substrates with electron-withdrawing functionality, we explored derivatization of enaminone **16c** to acetyl (**16d**), benzoyl (**16e**), tosyl (**16g**), and Boc (**16f**) accessorized products (Scheme 1.4B). The acylation of secondary enaminones using an amine base has previously been reported;[23a,25] however, exposure of intermediate **16c** to diisopropylethylamine (*i*-Pr_2NEt) and benzoyl chloride surprisingly produces diene **18** in 90% yield. We also examined other amine bases (e.g., pyridine and Et_3N), reagent equivalents, and the order of reagent addition, but in each case isolated a mixture of over acylated product and desired enaminone **16e**.[26] Similar results were obtained with acetyl chloride. The use of sodium hydride[27] eliminates over acylation, but provides enaminone **16e** with insufficient purity. Nevertheless, these conditions are amenable to the synthesis of tosyl enaminone **16g**, albeit in low yield.[28] The acylated and benzoylated enaminones (**16d** and **e**) can ultimately be obtained from iodoenone **19**[29] through a Buchwald coupling[30] and alkylation sequence (Scheme 1.4C). Boc functionalized enaminone **16f** is prepared without complication following the precedent of Hiemstra (Scheme 1.4B).[31]

Scheme 1.4. Preparation of enaminone alkylation precursors.



With a number of enaminones in hand, we screened a series of palladium-catalyzed decarboxylative allylic alkylation conditions (Table 1.2). Enaminone substrates that possess a hydrogen on the nitrogen (e.g., **16c** and **i**) generate a number of alkylation products with a Pd(PHOX) system and were consequently excluded from this study. The enaminone screen was performed in a manner similar to the previous investigation of lactams,[10,32] employing the ligands (*S*)-**3** and (*S*)-**8** and the same four solvents: tetrahydrofuran (THF), *tert*-butyl methyl ether (TBME), toluene, and 2:1 hexane–toluene.

Table 1.2. Enaminone allylic alkylation screen.[a]



					Enantiomeric Excess (% ee)[b]			
entry	substrate	R	product	ligand	THF	TBME	Toluene	2:1 Hex–Tol
1 2	*13a*	H	*21a*	*3* *8*	87 85	88 86	87 88	87 85
3 4	*14a*	O*i*-Bu	*22a*	*3* *8*	85 86	85 86	86 86	87 88
5 6	*16a*	NMe(Bn)	*23a*	*3* *8*	61 79	60 78	55 84	52 83
7 8	*16b*	NPh(Bn)	*23b*	*3* *8*	81 76	87 74	85 82	83 83
9 10	*16d*	NAc(Bn)	*23d*	*3* *8*	89 83	90 85	88 88	88 86
11 12	*16e*	NBz(Bn)	*23e*	*3* *8*	86 80	87 83	88 82	87 83
13 14	*16f*	NBoc(Bn)	*23f*	*3* *8*	87 84	86 84	87 81	82 83
15 16	*16g*	NTs(Bn)	*23g*	*3* *8*	84 82	83 83	83 83	82 83

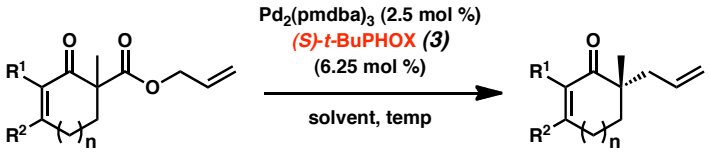
[a] *Conditions*: enone **13a**, vinylogous ester **14a**, or enaminone **16a, b, d–g** (1.0 equiv), $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in solvent (0.033 M) at 40 °C.
[b] Determined by GC, HPLC, or SFC analysis. Red = with *(S)*-(**3**) as ligand and blue = with *(S)*-(**8**) as ligand.

We made several observations upon analysis of the ligand, solvent, and substrate trends that distinguished this substrate class considerably from the previously examined lactams. First, enaminones are obtained in modestly better selectivity with (*S*)-**3** as a ligand in most solvents (entries 7–16), with the exception of methyl enaminone **23a**, which significantly favors (*S*)-**8** (entries 5–6). Second, no significant solvent trend is observed for enaminones overall. Third, electron-rich enaminones (i.e., **16a** and **b**) display decreased enantioselectivities and also require extended reaction times for completion,[33] while enaminones bearing electron-withdrawing substituents (**23d–g**) are all generated in 80–90% ee. By comparison, lactam substrates perform with much higher enantioselectivity with ligand (*S*)-**8** in non-polar solvents.[10,34] Furthermore, the modest distinction in enantioselectivity for the electron-withdrawing enaminones sharply contrasts with the corresponding lactam series, where the *N*-substituent plays a considerable role, producing significant variation in selectivity.[10,35] These differences suggest that the *N*-functional group does not contribute to enantioselectivity solely through a perturbation of enolate electronics.

Beyond these considerations, the most striking feature of the screen is that enantioselectivities observed for enaminones **23d–g** are approximately equivalent to results obtained for enone **21a**,[36] vinylogous ester **22a**, previously investigated vinylogous molecules (Table 1.3),[18b,19] and even more general ketone substrates. Of all the enaminones screened, acetyl variant **23d** provides the highest selectivity at 90% ee in TBME, which is only marginally better than the optimal values for the related vinylogous systems. The modest differences between these vinylogous molecules (i.e., **21–23**)

further suggest that the electronic nature of the enolate is not likely the predominant factor in providing high enantioselectivity for lactams and imides.

Table 1.3. Alkylation of other vinylogous esters and thioesters.[a]



14/24 and 15/25 ***22/27 and 26/28***

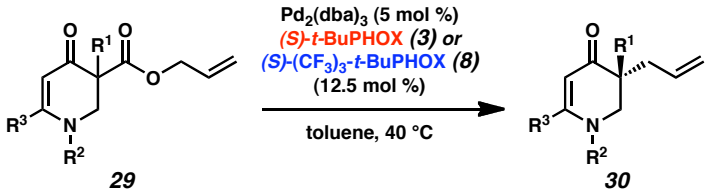
entry	substrate	n	R^1	R^2	product	solvent	temp (°C)	yield (%)	ee (%)[b]	ref.
1	***14b***	1	Me	O*i*-Bu	***22b***	toluene	80	86	75	19a
2	***15a***	1	Me	SPh	***26a***	toluene	50	85	92	19a
3	***15a***	1	Me	SPh	***26a***	benzene	50	61[c]	92	19a
4	***15a***	1	Me	SPh	***26a***	THF	50	88	92	19a
5	***15a***	1	Me	SPh	***26a***	1,4-dioxane	50	88	92	19a
6	***24a***	2	H	O*i*-Bu	***27a***	Et_2O	30	93	86	18b
7	***25a***	2	H	SPh	***28a***	Et_2O	30	86	89	18b

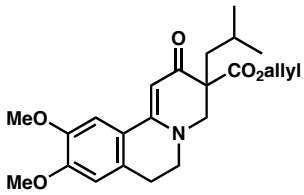
[a] *Conditions*: vinylogous ester **14**/**24** or vinylogous thioester **15**/**25**, $Pd_2(pmdba)_3$ (2.5 mol %), and *(S)-t*-BuPHOX (**3**) (6.25 mol %) in solvent at temp. [b] Determined by HPLC or SFC analysis. [c] β-Ketoester **15a** recovered in 26% yield.

While pursuing enaminones, we also briefly examined the related 2,3-dihydropyridin-4-ones, which possess the nitrogen within the ring (Table 1.4). Acylation and alkylation (or vice versa) of known dihydropyridinones[37,38,39] allows preparation of the reaction precursors **29a–d**. Under our standard palladium-catalyzed conditions, *N*-carboxybenzyl substituted product **30a** is formed with enantioselectivities similar to electronically related enaminones. Electron-rich 2,3-dihydropyridin-4-ones **30b** and **c** are curiously also generated in the same range. Even 2,3-dihydropyridin-4-one **30d** is produced in excellent enantioselectivity, despite the highly electron-rich nature of the

enolate. These results again allude to other factors beyond enolate electronics that direct alkylation selectivity.

Table 1.4. Allylic alkylation of 2,3-dihydropyridin-4-ones.[a]



entry	substrate *29*	R^1	R^2	R^3	product *30*	ligand	yield (%)	ee (%)[b]
1	*29a*	Me	Cbz	H	*30a*	*3*	80	86
2						*8*	98	84
3	*29b*	Me	Bn	H	*30b*	*3*	82	88
4						*8*	94	86
5	*29c*	*i*-Bu	Bn	H	*30c*	*3*	85	84
6						*8*	81	88
7	*29d*				*30d*	*8*	81	91

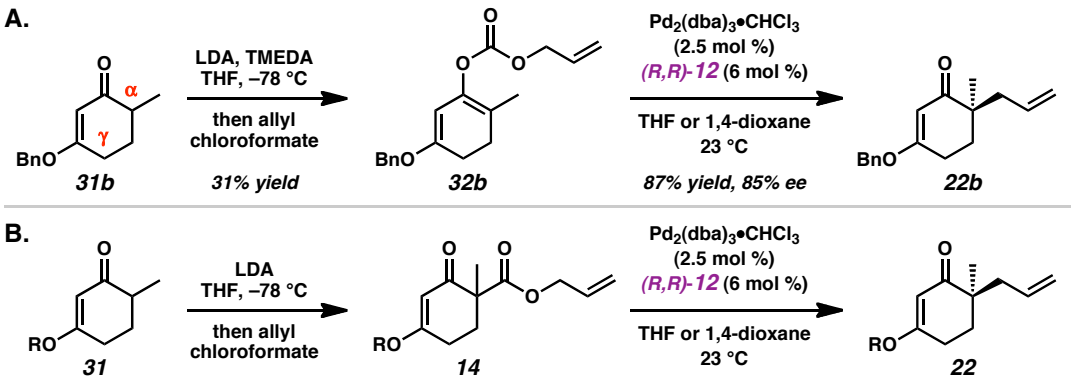
[a] *Conditions*: 2,3-dihydropyridin-4-ones **29**, $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in toluene (0.033 M) at 40 °C. [b] Determined by HPLC or SFC analysis. Red = with *(S)*-**3** as ligand and blue = with *(S)*-**8** as ligand.

1.2.1.1 Other Reports of Allylic Alkylation on Vinylogous Molecules

Trost has also reported the palladium-catalyzed allylic alkylation of vinylogous esters and thioesters employing their C_2-symmetric *P*,*P*-ligands. In particular, their 2006 study prepares a range of related α-quaternary vinylogous products using (*R*,*R*)-**12**.[20a] This effort first focused on the transformation of vinylogous esters into allyl enol carbonate alkylation precursors. However, enolate regioselectivity (α vs. γ deprotonation) is poor for a number of vinylogous alkoxy groups except benzyl (**32b**),

although this carbonate product is formed in low yield (Scheme 1.5A). Several β-ketoesters were alternatively examined, but lower conversions were observed with these substrates than with enol carbonate **32b** (Scheme 1.5B). The best results were obtained with phenyl and Boc substituted β-ketoesters (**14e** and **f**), which have decreased electron-donating contribution from the vinylogous oxygen. Trost consequently investigated the analogous thioesters, reasoning that sulfur would have less orbital overlap. Vinylogous thioester **14b** performs with good yield and perfect enantioselectivity (Scheme 1.6), and a variety of other thioesters are also produced with good to excellent ee. Trost has also examined exocyclic vinylogous esters and carried the enantioenriched products onto the natural products hamigeran B[20b,c] and allocyathin B_2.[20d]

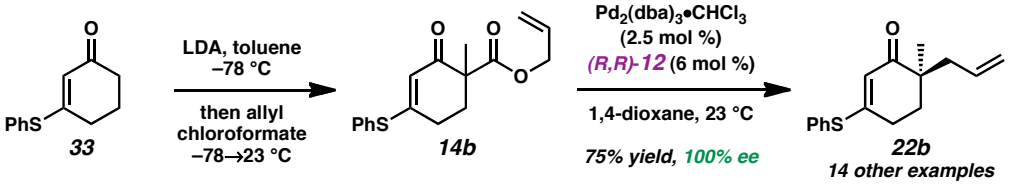
Scheme 1.5. Asymmetric allylic alkylation of vinylogous esters performed by Trost.



entry	substrate *31*	R^1	product *14*	yield (%)[b]	product *22*	yield (%)[b]	ee (%)[c]
1	*31b*	Bn	*14b*	87	*22b* [e]	51	91
2	*31c*	Et	*14c*	85	*22c* [d]	26	94
3	*31d*	*t*-Bu	*14d*	85	*22d* [d]	29	97
4	*31e*	Ph	*14e*	91	*22e* [d]	70	96
5	*31f*	Boc	*14f*	32	*22f* [e]	66	94

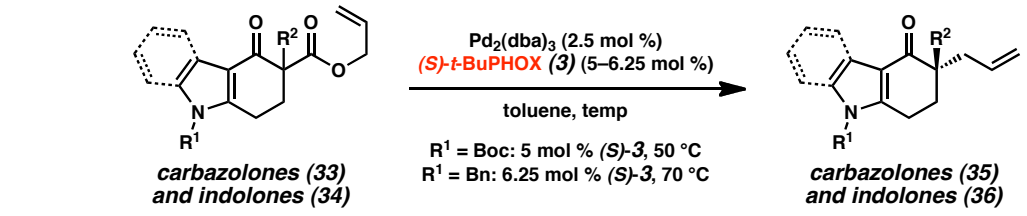
[a] *Conditions*: vinylogous ester **16**, $Pd_2(dba)_3$ (5 mol %), and *(R,R)*-**12** (6 mol %) in solvent (0.1 M) at 23 °C. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 1,4-dioxane as solvent. [e] THF as solvent.

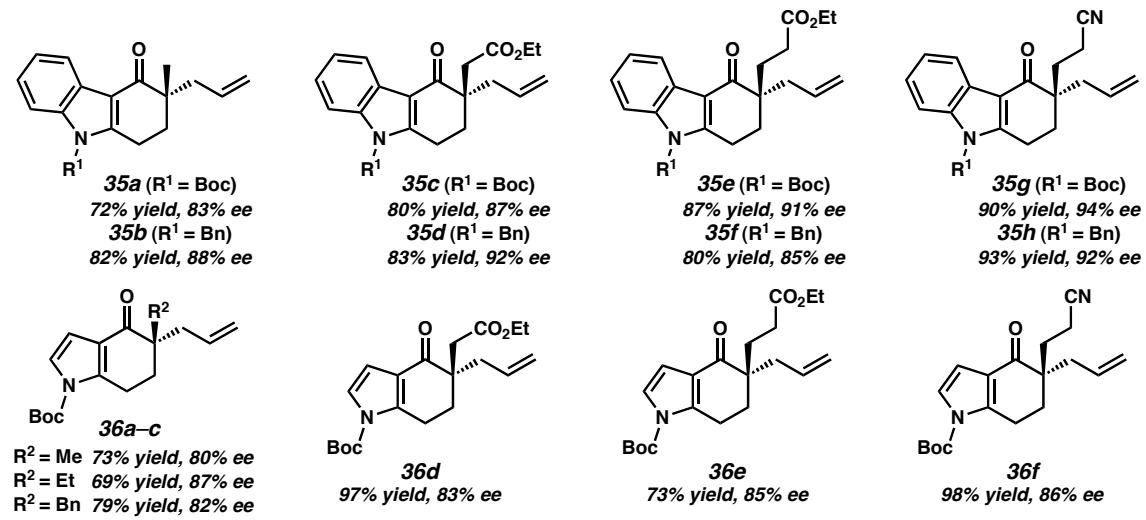
Scheme 1.6. Asymmetric allylic alkylation of vinylogous thioesters performed by Trost.



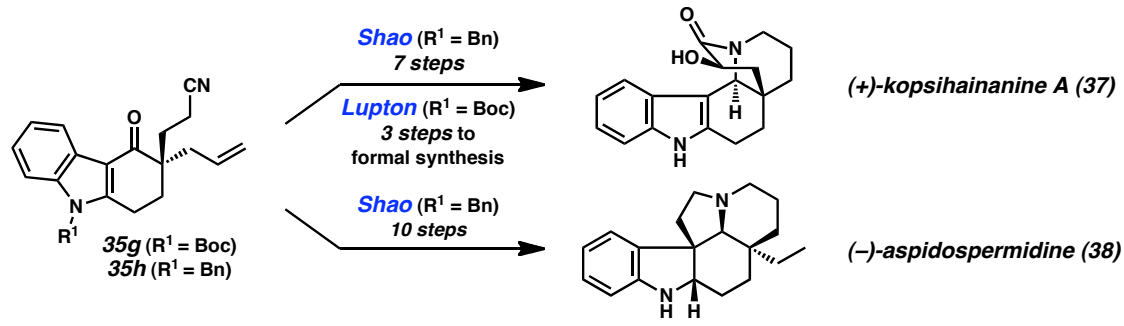
Concurrent with our efforts on enaminones, Lupton[40] and Shao[41] independently published sequential reports on the Pd-catalyzed allylic alkylation of two other vinylogous amide classes, carbazolones (**33**) and indolones (**34**) (Scheme 1.7). The reaction parameters between the two papers are almost identical (Lupton: 5 mol% ligand, 50 °C; Shao: 6.25 mol % ligand, 70 °C)[42] and many of the substrates are also related. In these efforts, Lupton selects a Boc *N*-protecting group, while Shao employs a benzyl substituent. The enantioselectivities of the methyl/allyl α-quaternary carbazolones (**35a** and **b**) and indolones (**36a**) are comparable to our results with enaminones that possess electron-withdrawing functionality. Even the *N*-benzyl carbazolones are produced in good to excellent ee, unlike the enaminones that bear electron-rich groups (**23a** and **b**). In addition to screening several alkylation precursors, both laboratories advance their enriched cyanide alkylation products (**35g** and **h**) onto (+)-kopsihainanine A (**37**) through total and formal synthetic routes, and Shao also completes the alkaloid (–)-aspidospermidine (**38**, Scheme 1.8).

Scheme 1.7. Alkylation of carbazolone (Lupton, R^1 = Boc; Shao, R^1 = Bn) and indolone (Lupton) substrates reported in 2013.





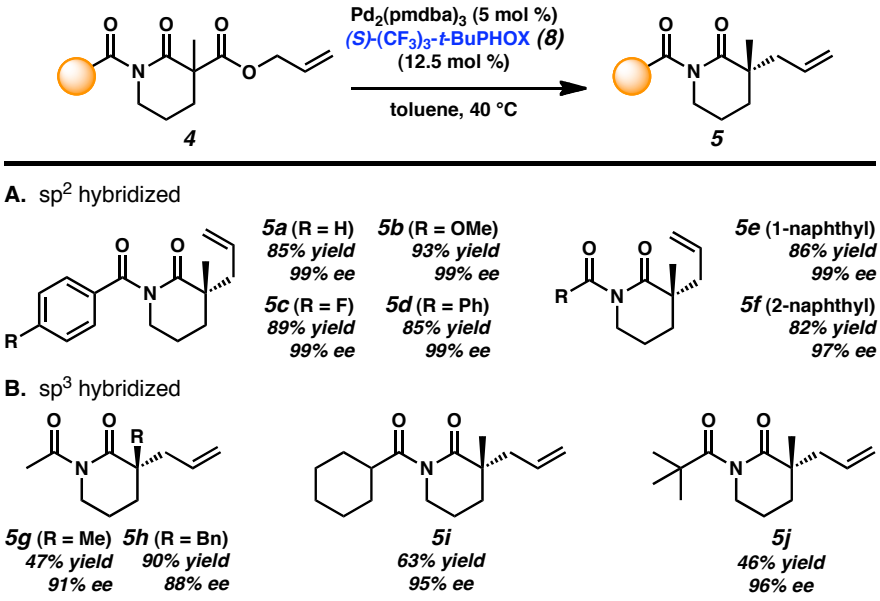
*Scheme 1.8. Derivatization of cyanides **35g** and **h** to alkaloid natural products.*



1.2.2 α'-Functionalized Substrates

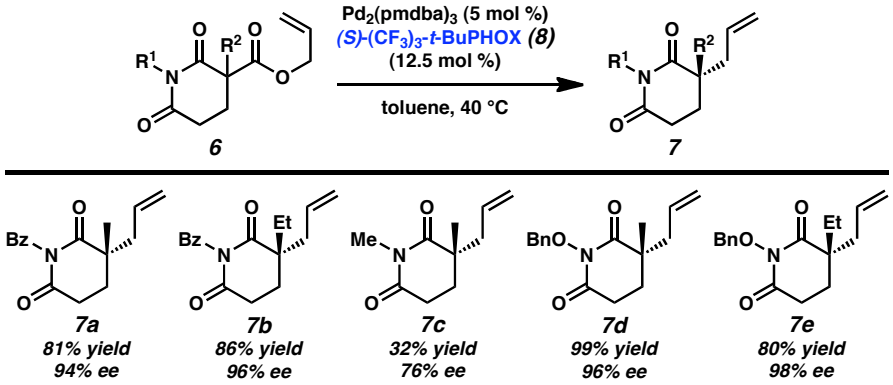
Having investigated the impact of enolate electronics, we diverted our efforts to study the influence of α'-functionality on alkylation selectivity (Scheme 1.9). Our previous lactam screen identified the benzoyl moiety as the optimal protecting group,[10] providing high to nearly perfect enantioselectivities for a variety of lactams (e.g., **5a**). Interestingly, both electron-rich and electron-poor benzoyl lactams (**5b–d**) as well as naphthoyl lactams (**5e** and **f**) display excellent ee, whereas acetyl lactams (e.g., **5g** and **h**) provide lower selectivity. This prompted us to question whether these results are due to a hybridization or steric effect. Consequently, we synthesized the bulky sp^3 hybridized cyclohexoyl lactam **4i** and pivaloyl lactam **4j**, which proceed in improved enantioselectivities compared to analogous acetyl lactam **4g**, supporting a steric effect.[43]

Scheme 1.9. Impact of various sp^3 and sp^2 acyl groups on allylic alkylation enantioselectivity for lactams.



In conjunction with our investigation of the asymmetric allylic alkylation of lactams, we found that *N*-benzoyl cyclic imides **7a** and **b** are furnished in excellent ee (Scheme 1.10). However, we observed that formation of *N*-methyl imide **7c** proceeds with moderate enantioselectivity and is hampered by low reactivity.[43] As this substrate also generates an intermediate imido enolate (as do lactams **5a**–**j**, Scheme 1.9), this result further supports our conclusion that enolate electronics do not play a major role in the enhanced enantioselectivities observed for *N*-benzoyl lactams. As such, we examined the influence of alternate *N*-substituents in the context of the allylic alkylation with imides.

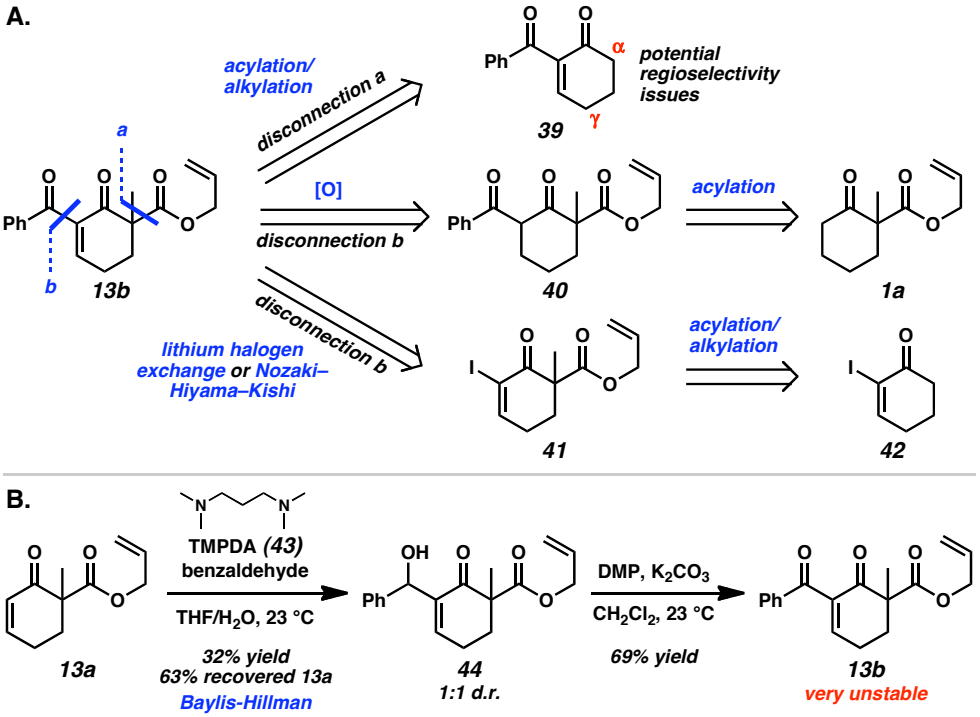
Scheme 1.10. Allylic alkylation of cyclic imides.



Gratifyingly, we identified *N*-benzyloxy imides as excellent substrates for this methodology, generating imides **7d** and **e** in yields and enantioselectivities comparable to their *N*-benzoyl counterparts. In conjunction with the results obtained for substituted *N*-acyl lactams **5g**–**j**, we reason that the nature of the α'-substituent leads to the observed enhancements in enantioselectivity, though enolate electronics have been shown to dramatically affect the reaction rate.

We sought to further probe the α'-group contribution without the influence of nitrogen and consequently focused on a series of α'-functionalized enones, including benzoyl enone **13b** (Scheme 1.11). Previous research suggested enolization regioselectivity issues may arise in acylating/alkylating enone **39** (α vs. γ, path A),[6b] prompting us to pursue approaches to enone **13b** through retrosynthetic disconnection of the benzoyl substituent (path B). Unfortunately, attempts to acylate and oxidize β-ketoester **1a** proved unsuccessful. Both lithium halogen exchange and Nozaki–Hiyama–Kishi coupling on iodoenone **41** also failed to install the benzoyl group. The synthesis of enone **13b** is ultimately possible via a Baylis–Hillman[44] reaction and oxidation sequence (Scheme 1.11B). A number of oxidants were examined in the latter transformation, but only Dess–Martin periodinane (DMP) proved successful. Benzoyl enone **13b** is very sensitive to alkene isomerization, and thus the addition of potassium carbonate as a buffer and the use of triethylamine deactivated silica gel for purification are necessary. Although we were able to prepare enone **13b**, stability issues make this molecule a poor alkylation substrate and prohibit the isolation of the desired methyl/allyl α-quaternary enone under our standard palladium-catalyzed conditions.

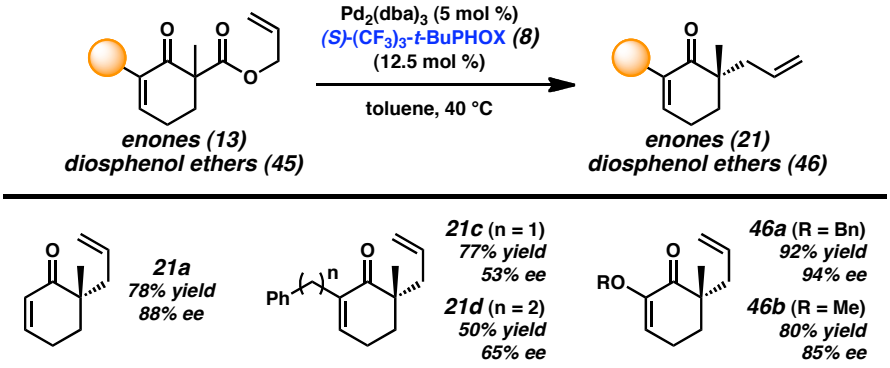
Scheme 1.11. Retrosynthetic approaches and successful route to benzoyl enone ***13b****.*



Despite the complications with benzoyl enone **13b**, we were able to synthesize enones **13c** and **d** and diosphenol ethers **45a** and **b** under standard acylation/alkylation conditions. To examine the relative merit of the steric and stereoelectronic effects associated with the α'-substituent, we subjected these substrates to the palladium-catalyzed alkylation parameters employed with lactams and imides (Scheme 1.12). In this transformation, enones **21c** and **d** are formed in low enantioselectivity. By contrast, benzyl diosphenol ether **46a**, which differs from **21d** only in the substitution of oxygen for a methylene group, is generated in 92% yield and 94% ee. This suggests that purely steric or π-stacking interactions are not the sole contributing factors to enantioselectivity. Rather, electronic effects of the α'-substituent exert an important influence on the stereoselectivity of the reaction. However, a certain amount of steric bulk appears critical

in obtaining high enantioselectivity as methyl diosphenol ether **46b** is produced in 85% ee. In comparison, analogous enone **21a**, which bears no α'-functionality, proceeds under the same conditions to afford enone **21a** in 88% ee,[36] with vinylogous amides and esters also in the ~80–90% ee range (*vide supra*). Overall, our studies on the role of the α'-substituent have culminated in the discovery of substrate **45a**, which proceeds with the greatest enantioselectivity observed in a Pd(PHOX) catalyst system for a carbocyclic substrate bearing an α-methyl and unsubstituted allyl moiety.

Scheme1.12. Allylic alkylation of α'-functionalized enones and diosphenol ethers.



1.3 CONCLUDING REMARKS

In summary, we have designed and evaluated a number of novel substrates to probe the influence of enolate electronics and the role of α'-functionality on selectivity in the palladium-catalyzed decarboxylative allylic alkylation. Based on these results, we reason that the high enantioselectivities observed with lactams and imides are a consequence of both electronic and steric effects associated with α'-substituents, and that enolate electronics alone contribute relatively little to the stereochemical outcome of the

reaction. Both experimental and theoretical investigations are currently underway in our group to determine the nature and origin of the effect of α'-substitution on this transformation and to use this insight to improve and expand our methods.

1.4 EXPERIMENTAL SECTION

1.1.1 MATERIALS AND METHODS

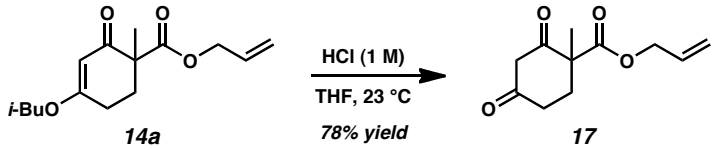
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[45] Acetone was used directly from a Sigma-Aldrich ACS reagent grade bottle. Brine solutions are saturated aqueous solutions of sodium chloride. Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. (*S*)-*t*-BuPHOX (**3**),[5ab] (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**),[5c] and allyl cyanoformate[46] were prepared by known methods. Reaction temperatures were controlled by an IKAmag temperature modulator. Reaction progress was monitored by thin-layer chromatography (TLC). TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. ICN silica gel (particle size 0.032-0.0653 mm) was used for flash column chromatography. Preparative HPLC purification was performed on an Agilent 1200 Series HPLC using an Agilent Prep-SIL column (5 μm, 30 x 250 mm) at ambient temperature with a flow rate of 50 mL/min. Separation was monitored by UV (λ = 254 nm) and fractions were collected at the valleys between peaks. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or benzene-d_6 (δ 7.16 ppm). ^{13}C NMR spectra are recorded on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer (75 or 125 MHz respectively) and are reported relative to $CDCl_3$ (δ 77.16 ppm) or benzene-d_6 (δ 128.06

ppm). Variable temperature NMR experiments were performed on a Varian Inova 500 MHz spectrometer and are reported relative to residual DMSO (δ 2.50 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, dm = doublet of multiplets, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent, *ee*). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak (AD, AD-H, or AS) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral SFC was performed with a JASCO 2000 series instrument or a Thar SFC utilizing Chiralpak (AD-H or AS-H) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm), or a Chiralpak IC column (4.6 mm x 10 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (GC-EI+, EI+, or FAB+) or Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

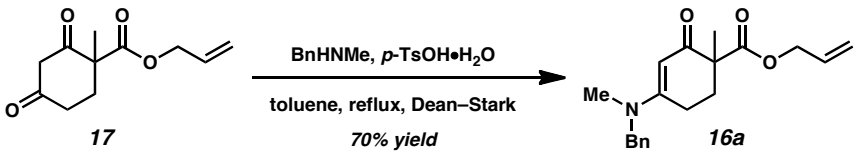
1.4.2 PREPARTIVE PROCEDURES

1.4.2.2 Preparation of Compounds Related to Enaminone Screen

1.4.2.2.1 *Enaminone Allylic Alkylation Precursors*

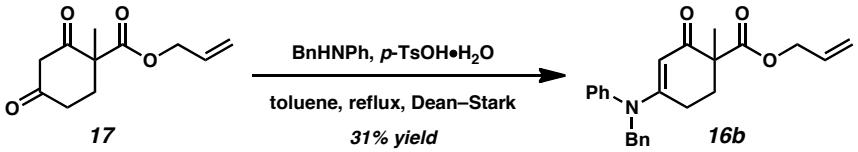


Dione 17. Procedure adapted from report by Desmaële.[21] A 100 mL round-bottom flask equipped with a magnetic stir bar was charged with vinylogous ester **14a**[18c] (3.08 g, 11.58 mmol, 1.00 equiv), THF (30 mL, 0.39 M), and aq HCl (1 M in H_2O, 14.00 mL, 14.00 mmol, 1.21 equiv). The reaction mixture was initially a suspension that developed into a solution over time. After 7 h of vigorous stirring at ambient temperature, the reaction was diluted with EtOAc (30 mL) and transferred to a separatory funnel where the aqueous layer was extracted seven times with EtOAc. The combined organics (400 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 31 x 5 cm, 100% hexanes→20%→50% EtOAc in hexanes) to afford dione **17** (1.89 g, 11.58 mmol, 78% yield) as a pale yellow oil; R_f = 0.17 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) mixture of keto-enol tautomers, see spectra section; IR (Neat Film NaCl) 3500–2500 (broad stretch), 3088, 2983, 2939, 2657, 2591, 1734, 1595, 1457, 1413, 1383, 1358, 1343, 1309, 1272, 1249, 1190, 1114, 986, 932, 853 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{15}O_4$ $[M+H]^+$: 211.0965, found 211.0966.



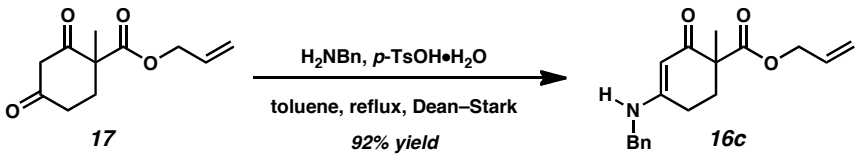
Enaminone 16a. A 50 mL round-bottom flask containing a magnetic stir bar was charged with dione **17** (465.4 mg, 2.21 mmol, 1.00 equiv), toluene (24 mL, 0.09 M), benzylmethylamine (320 µL, 2.48 mmol, 1.12 equiv), and *p*-toluenesulfonic acid monohydrate (42.3 mg, 0.22 mmol, 10 mol %). The flask was equipped with a Dean–Stark trap and water condenser and was lowered into a preheated oil bath (135 °C). After 2 h of refluxing, the solution was removed from the oil bath and allowed to cool to room temperature. The solution was quenched with a sat. Na_2CO_3 solution (20 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics (200 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27 x 3 cm, 100% hexanes→20%→50%→60%→70% EtOAc in hexanes) to afford enaminone **16a** (484.8 mg, 1.55 mmol, 70% yield) as a yellow/orange oil; R_f = 0.24 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2H), 7.32–7.27 (m, 1H), 7.09 (d, J = 7.4 Hz, 2H), 5.93–5.83 (m, 1H), 5.29 (dq, J = 17.3, 1.5 Hz, 1H), 5.26 (s, 1H), 5.18 (dq, J = 10.5, 1.4 Hz, 1H), 4.66–4.56 (m, 2H), 4.51 (s, 2H), 2.96 (s, 3H), 2.74–2.63 (m, 1H), 2.56–2.45 (m, 2H), 1.95–1.84 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ193.9, 173.7, 164.3, 132.2, 129.1, 127.8, 126.7, 118.0, 98.1, 65.6, 55.2, 51.1, 38.5, 32.6, 24.4, 21.0; IR (Neat Film NaCl) 3063, 3028, 2933, 2873, 1733, 1615, 1585, 1563, 1557, 1495, 1455, 1415, 1377, 1352, 1332, 1295, 1258, 1222,

1203, 1174, 1113, 1028, 989, 929, 821, 735 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found 314.1754.



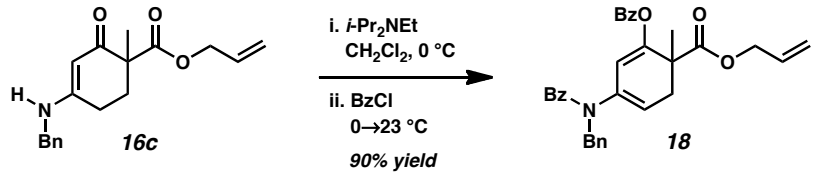
Enaminone 16b. A 50 mL round-bottom flask containing a magnetic stir bar was charged with dione **17** (500.3 mg, 2.38 mmol, 1.00 equiv), toluene (24 mL, 0.10 M), benzylphenylamine (480.0 mg, 2.62 mmol, 1.10 equiv), and *p*-toluenesulfonic acid monohydrate (45.6 mg, 0.24 mmol, 10 mol %). The flask was equipped with a Dean–Stark trap and water condenser and was lowered into a preheated oil bath (135 °C). After 8 h of refluxing, the solution was removed from the oil bath and allowed to cool to room temperature. The solution was quenched with a sat. Na_2CO_3 solution (20 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics (200 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified twice by flash column chromatography (SiO_2, 26 x 3 cm, 100% hexanes→10%→15%→20%→30%→40% EtOAc in hexanes ***then*** SiO_2, 26.5 x 3 cm, 100% hexanes→ 5%→10%→15% →20%→30%→ 50% EtOAc in hexanes) to afford enaminone **16b** (276.6 mg, 0.74 mmol, 31% yield) as a yellow oil; R_f = 0.50 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2H), 7.33–7.24 (m, 4H), 7.21–7.18 (m, 2H), 7.13–7.10 (m, 2H), 5.90 (dddd, J = 17.2, 10.7, 5.4, 5.4 Hz, 1H), 5.39 (s, 1H), 5.31 (dq, J = 17.2, 1.6 Hz, 1H), 5.21 (dq, J = 10.5, 1.4 Hz, 1H), 4.83 (s, 2H), 4.68–4.63 (m, 1H), 4.62–4.57 (m, 1H),

2.55–2.47 (m, 1H), 2.42 (ddd, J = 13.3, 6.1, 4.9 Hz, 1H), 2.33–2.27 (m, 1H), 1.84 (ddd, J = 13.5, 8.7, 4.9 Hz, 1H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 173.3, 163.9, 144.3, 136.4, 132.2, 129.9, 128.9, 128.0, 127.9, 127.7, 127.1, 118.0, 100.4, 65.6, 56.8, 51.6, 32.9, 25.9, 21.0; IR (Neat Film NaCl) 3061, 3031, 2975, 2933, 2872, 1734, 1623, 1560, 1494, 1453, 1426, 1408, 1377, 1346, 1327, 1293, 1255, 1210, 1174, 1112, 1080, 1061, 1022, 989, 929, 885, 825, 779, 733, 702 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{26}NO_3$ $[M+H]^+$: 376.1907, found 376.1903.



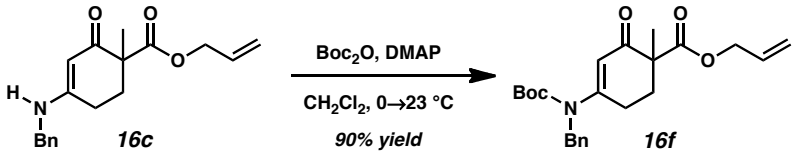
Enaminone 16c. A 250 mL round-bottom flask containing a magnetic stir bar was charged with dione **17** (1.89 g, 8.98 mmol, 1.00 equiv), toluene (90 mL, 0.10 M), benzylamine (1.1 mL, 10.04 mmol, 1.12 equiv), and *p*-toluenesulfonic acid monohydrate (169.0 mg, 0.89 mmol, 10 mol %). The flask was equipped with a Dean–Stark trap and water condenser and was lowered into a preheated oil bath (135 °C). After 5.5 h of refluxing, the solution was removed from the oil bath and allowed to cool to room temperature. The solution was quenched with a sat. Na_2CO_3 solution (50 mL) and transferred to a separatory funnel where the aqueous layer was extracted once with Et_2O and three times with dichloromethane. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 31 x 5 cm, 100% hexanes→20%→50% EtOAc in hexanes) to afford enaminone **16c** (2.48 g, 8.28 mmol, 92% yield) as a yellow solid; R_f =

0.27 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 3H), 7.29 (s, 2H), 5.95–5.82 (m, 1H), 5.30 (dq, J = 17.2, 1.6 Hz, 1H), 5.22 (s, 1H), 5.20 (dq, J = 10.5, 1.4 Hz, 1H), 4.62 (tt, J = 5.6, 1.5 Hz, 2H), 4.56 (br s, 1H), 4.24 (d, J = 5.0 Hz, 2H), 2.59 (ddd, J = 16.5, 8.8, 4.9 Hz, 1H), 2.50 (ddd, J = 13.3, 6.2, 4.9 Hz, 1H), 2.33 (dt, J = 16.6, 5.3 Hz, 1H), 1.91 (ddd, J = 13.6, 8.8, 5.0 Hz, 1H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 173.4, 162.6, 136.7, 132.2, 129.1, 128.2, 128.0, 118.0, 96.7, 65.6, 52.1, 47.5, 32.4, 26.7, 21.1; IR (Neat Film NaCl) 3260, 3064, 2978, 2933, 2868, 1730, 1576, 1545, 1452, 1427, 1375, 1359, 1297, 1253, 1218, 1199, 1172, 1107, 1028, 987, 929, 822, 735 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{18}H_{21}NO_3$ $[M+\bullet]^+$: 299.1521, found 299.1522.



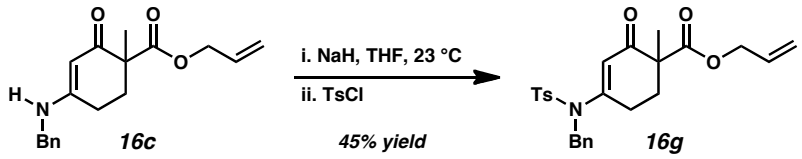
Diene 18. A 1 dram (4 mL) vial equipped with a stir bar and Teflon septa was charged with enaminone **16c** (49.9 mg, 0.167 mmol, 1.00 equiv) and lowered into a 0 °C bath (ice/water). Dichloromethane (1.7 mL, 0.10 M), *i*-Pr_2NEt (150 μL, 0.861 mmol, 5.17 equiv), and benzoyl chloride (40 μL, 0.345 mmol, 2.07 equiv) were added and the reaction was allowed to warm to room temperature over time. After 13 h, TLC analysis indicated consumption of starting material. The reaction was subsequently quenched with water (5 mL) and the aqueous layer was extracted four times with dichloromethane. The combined organics (50 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 26 x 1 cm, 5%→10%→15% EtOAc in hexanes) to afford diene **18** (75.8 mg, 0.149 mmol,

90% yield) as a yellow oil; R_f = 0.77 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07–8.02 (m, 2H), 7.65–7.59 (m, 1H), 7.56–7.51 (m, 2H), 7.50–7.45 (m, 2H), 7.39 (s, 2H), 7.37–7.32 (m, 3H), 7.32–7.30 (m, 2H), 7.28–7.24 (m, 1H), 6.20 (s, 1H), 5.81–5.72 (m, 1H), 5.22 (dt, J = 17.2, 1.4 Hz, 1H), 5.13 (dt, J = 10.3, 1.3 Hz, 1H), 4.97–4.79 (m, 3H), 4.56–4.43 (m, 2H), 2.75 (dd, J = 17.4, 4.6 Hz, 1H), 2.03 (dd, J = 17.4, 4.7 Hz, 1H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 170.7, 164.0, 150.5, 137.2, 136.2, 136.1, 133.9, 131.7, 130.2, 130.0, 129.4, 129.0, 128.8, 128.5, 128.3, 128.1, 127.5, 120.2, 118.6, 113.4, 66.1, 50.6, 46.4, 35.1, 20.4; IR (Neat Film NaCl) 3062, 3030, 2981, 2934, 1740, 1646, 1600, 1577, 1495, 1451, 1400, 1349, 1326, 1244, 1176, 1145, 1112, 1077, 1050, 1023, 1001, 980, 935, 824, 797, 755 cm^{-1}; HRMS (MM: ESI-APCI+) calc'd for $C_{32}H_{30}O_5N$ $[M+H]^+$: 508.2118, found 508.2122.



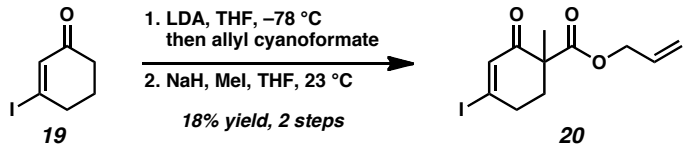
Enaminone 16f. A flame-dried 25 mL round-bottom flask containing a magnetic stir bar was loaded with enaminone **16c** (300.1 mg, 1.00 mmol, 1.00 equiv) and 4-dimethylaminopyridine (9.5 mg, 0.078 mmol, 7.8 mol %). The flask was charged with dichloromethane (10 mL, 0.10 M) and lowered into a 0 °C bath (ice/water). Di-*tert*-butyl dicarbonate (252.7 mg, 1.16 mmol, 1.15 equiv) was added, and the solution transitioned from yellow to clear. The ice bath was allowed to expire as the reaction was stirred overnight. After 22 h, the stir bar was removed from the flask, the reaction contents were concentrated under reduced pressure, and the resulting crude oil was purified by flash

column chromatography (SiO_2, 26.5 x 3 cm, 100% hexanes→5%→10%→15%→20% EtOAc in hexanes) to afford enaminone **16f** (360.0 mg, 0.90 mmol, 90% yield) as a pale yellow oil; R_f = 0.79 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.28 (m, 2H), 7.26–7.21 (m, 1H), 7.16–7.12 (m, 2H), 5.85 (dddd, J = 17.2, 10.5, 5.5, 5.5 Hz, 1H), 5.73 (t, J = 0.9 Hz, 1H), 5.27 (dq, J = 17.2, 1.6 Hz, 1H), 5.20 (dq, J = 10.5, 1.3 Hz, 1H), 4.80 (s, 2H), 4.58 (dddd, J = 5.6, 2.8, 1.5, 1.5 Hz, 2H), 2.92–2.77 (m, 2H), 2.45 (dt, J = 13.5, 5.3 Hz, 1H), 1.86 (ddd, J = 13.5, 7.7, 5.7 Hz, 1H), 1.42 (s, 9H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 172.6, 162.2, 152.9, 137.2, 131.9, 128.8, 127.5, 126.3, 118.3, 114.8, 83.0, 65.8, 53.0, 52.5, 33.6, 28.1, 27.5, 20.4; IR (Neat Film NaCl) 3090, 3064, 3034, 2978, 2935, 2873, 1718, 1662, 1654, 1595, 1497, 1453, 1425, 1369, 1344, 1317, 1300, 1248, 1210, 1150, 1113, 1029, 989, 937, 856, 815, 769, 737 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2118, found 400.2127.



Enaminone 16g. A flame-dried 25 mL round-bottom flask containing a magnetic stir bar was cycled into a glove box and loaded with sodium hydride (95% by weight, 32.6 mg, 1.29 mmol, 1.29 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, and charged with THF (6 mL). Enaminone **16c** (300.3 mg, 1.00 mmol, 1.00 equiv) was added in one portion and the grey suspension bubbled and became a yellow solution over time. The flask was rinsed with additional THF (4 mL, 10 mL total, 0.10 M). The reaction was stirred vigorously for 70 min before *p*-toluenesulfonyl

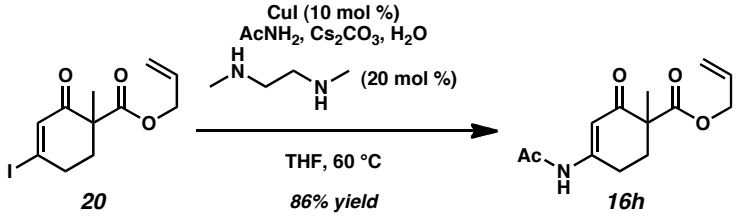
chloride (287.6 mg, 1.51 mmol, 1.50 equiv) was added in one portion. After 6 h, the flask was lowered into a 0 °C bath (ice/water) and quenched with water (reaction mixture bubbled). The mixture was transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics (100 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27 x 3 cm, 100% hexanes→5%→10%→15%→ 50% EtOAc in hexanes) to afford enaminone **16g** (203.8 mg, 0.45 mmol, 45% yield) as a yellow oil; R_f = 0.68 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.33–7.25 (m, 3H), 7.23 (d, J = 6.6 Hz, 2H), 5.75 (dddd, J = 17.3, 10.8, 5.6, 5.6 Hz, 1H), 5.68 (t, J = 1.1 Hz, 1H), 5.24–5.15 (m, 2H), 4.81–4.69 (m, 2H), 4.48 (dddd, J = 13.5, 5.6, 1.4, 1.4 Hz, 1H), 4.40 (dddd, J = 13.2, 5.6, 1.4, 1.4 Hz, 1H), 2.67–2.55 (m, 2H), 2.46 (s, 3H), 2.32 (dt, J = 13.9, 5.2 Hz, 1H), 1.69 (ddd, J = 13.8, 8.0, 5.9 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 171.9, 158.4, 144.8, 135.6, 135.3, 131.7, 130.2, 128.9, 128.1, 127.6, 127.5, 119.5, 118.5, 65.9, 53.0, 52.2, 32.4, 27.9, 21.8, 20.0; IR (Neat Film NaCl) 3064, 3032, 2981, 2935, 2873, 1735, 1669, 1596, 1496, 1454, 1424, 1359, 1321, 1292, 1255, 1164, 1115, 1089, 1058, 1028, 984, 910, 883, 816, 773, 743 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{28}NSO_5$ $[M+H]^+$: 454.1683, found 454.1691.



β-Iodoenone 20. A 200 mL round-bottom flask equipped with a magnetic stir bar was charged with diisopropyl amine (1.52 mL, 10.85 mmol, 1.19 equiv) and THF (36 mL). The flask was lowered into a 0 °C bath (ice/water) and *n*-BuLi (4.5 mL, 2.3 M in hexanes, 10.35 mmol, 1.14 equiv) was added dropwise over several minutes. The reaction was stirred for 15 min before the ice bath was removed and replaced with a –78 °C bath (dry ice/acetone). β-Iodoenone **19**[29] (2.00 g, 9.09 mmol, 1.00 equiv) was transferred via cannula to the flask using several THF rinses (1 x 14 mL and 2 x 5 mL rinses, total added = 60 mL, 0.15 M), producing a yellow solution that transitioned to red over time. The reaction was stirred for 1 h before allyl cyanoformate (1.12 mL, 10.38 mmol, 1.14 equiv) was added dropwise. After 2.25 h, the reaction was quenched with sat. NH_4Cl solution and allowed to warm to room temperature. The reaction contents were transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was filtered through a short silica gel plug to afford an orange oil.

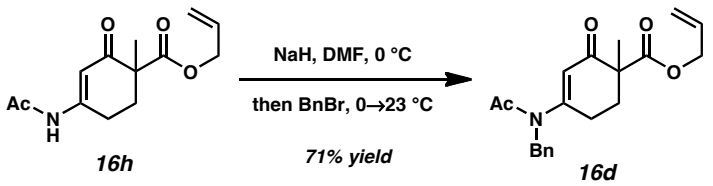
A 50 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box and loaded with sodium hydride (161.0 mg, 95% by weight, 6.37 mmol, 1.21 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, and charged with THF (6 mL). The crude orange oil from the previous step (1.61 g, 5.27 mmol, 1.00 equiv) was transferred via cannula to the flask using several THF rinses (1 x

5 mL + 3 x 2 mL, total added = 21.0 mL, 0.25 M). The grey suspension bubbled and became a yellow solution that transitioned to red over time. The reaction was stirred for 30 min before methyl iodide (400 μL, 6.43 mmol, 1.22 equiv) was added dropwise. After 3.5 h, the reaction was quenched with water and extracted four times with dichloromethane. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28.5 x 4 cm, 100% hexanes→5% EtOAc in hexanes) to afford β-Iodoenone **20** (536.3 mg, 1.68 mmol, 18% yield over two steps) as a yellow oil; R_f = 0.72 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (dd, J = 2.2, 1.2 Hz, 1H), 5.94–5.79 (m, 1H), 5.32–5.26 (m, 1H), 5.24 (dt, J = 10.5, 1.1 Hz, 1H), 4.67–4.56 (m, 2H), 3.05–2.96 (m, 1H), 2.93–2.85 (m, 1H), 2.43 (dt, J = 13.8, 4.9 Hz, 1H), 1.95 (ddd, J = 14.0, 9.0, 5.3 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 171.7, 139.6, 131.6, 125.5, 118.8, 66.1, 52.7, 38.6, 35.0, 20.3; IR (Neat Film NaCl) 3084, 2982, 2936, 2868, 1732, 1682, 1597, 1455, 1424, 1378, 1333, 1295, 1246, 1169, 1098, 1033, 986, 926, 852, 770, 737 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{14}O_3I$ $[M+H]^+$: 320.9982, found 320.9981.



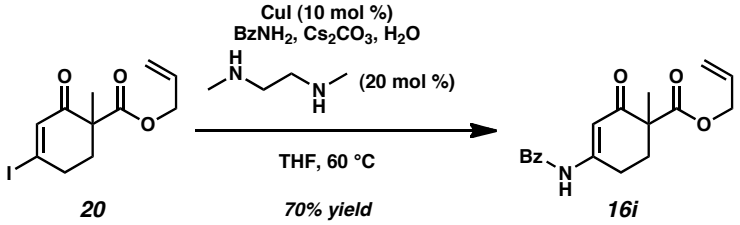
Enaminone 16h. Adapted from procedure by Buchwald.[30] CuI (24 mg, 0.13 mmol, 0.10 equiv), Cs_2CO_3 (624 mg, 1.92 mmol, 1.50 equiv) and acetamide (91 mg, 1.5 mmol, 1.2

equiv) were added to a 25 mL Schlenck bomb equipped with a stir bar under argon atmosphere. The Schlenck bomb was evacuated and backfilled with argon three times. A solution of vinyl iodide **20** (409 mg, 1.28 mmol, 1.00 equiv), *N,N'*-dimethylethylenediamine (23 mg, 0.26 mmol, 0.20 equiv) and nanopure water (23 mg, 1.3 mmol, 1.0 equiv) in THF (2.6 mL, 0.5 M) was added via syringe. The reaction flask was lowered into a 60 °C oil bath. After 12 h of stirring, TLC analysis indicated complete conversion of starting material. The reaction was subsequently diluted with 15 mL CH_2Cl_2, transferred to a separatory funnel and washed twice with 5% aqueous NH_4OH (10 mL). The combined aqueous layers were extracted twice with CH_2Cl_2 (15 mL). The combined organics were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 12 x 3 cm, 20→33→50→67% EtOAc in hexanes) to afford enaminone **16h** (276 mg, 1.10 mmol, 86% yield) as a pale yellow oil; R_f = 0.10 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 6.60 (s, 1H), 5.90–5.77 (m, 1H), 5.27 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.58 (dq, *J* = 5.6, 1.3 Hz, 2H), 2.78 – 2.64 (m, 1H), 2.62–2.43 (m, 1H), 2.54–2.45 (m, 1H), 2.11 (s, 3H), 2.02–1.83 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 172.5, 169.9, 155.9, 131.7, 118.5, 110.1, 65.9, 52.3, 31.9, 25.7, 25.0, 20.6; IR (Neat Film NaCl) 3299, 3135, 2937, 1728, 1626, 1520, 1456, 1426, 1370, 1259, 1220, 1184, 1114, 999, 939, 877 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{13}H_{18}NO_4$ $[M+H]^+$: 252.1230, found 252.1219.

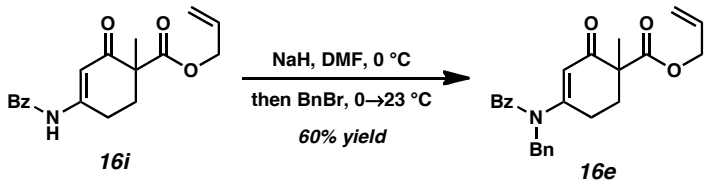


Enaminone 16d. In a 5 mL round bottom flask equipped with a stir bar under nitrogen atmosphere, enaminone **16h** (63 mg, 0.25 mmol, 1.0 equiv) was taken up in dry DMF (2.8 mL, 0.089 M) and cooled to 0 °C with an ice/water bath. Sodium hydride (60% suspension in mineral oil, 12 mg, 0.30 mmol, 1.2 equiv) was added to the mixture, accompanied by the formation of bubbles. The reaction was stirred for 1 h before the dropwise addition of benzyl bromide (36 μL, 0.30 mmol, 1.2 equiv) by syringe. The reaction temperature was maintained at 0 °C for 5 h before allowing the ice bath to gradually expire. After an additional 6 h at 23 °C, TLC analysis indicated complete conversion of starting material. The reaction was subsequently diluted with EtOAc (10 mL) and sat. NH_4Cl sol. (10 mL) and transferred to a separatory funnel. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted twice with EtOAc (2 x 10 mL). The combined organics were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 15 x 3 cm, 20% acetone in hexanes) to afford enaminone **16d** (61 mg, 0.18 mmol, 71% yield) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 7.29–7.24 (m, 1H), 7.19–7.16 (m, 2H), 5.87–5.79 (m, 1H), 5.78 (s, 1H), 5.27 (dt, J = 17.2, 1.4 Hz, 1H), 5.21 (dt, J = 10.5, 1.3 Hz, 1H), 4.89–4.84 (m, 1H), 4.78–4.72 (m, 1H), 4.56 (dt, J = 5.7, 1.3 Hz, 2H), 2.58 (ddd, J = 9.3, 4.9, 1.6 Hz, 1H), 2.56–2.48 (m, 1H), 2.44 (dtd, J = 13.8, 4.8, 1.2 Hz, 1H), 2.16 (s, 3H), 1.87–1.78 (m, 1H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 172.0, 170.0,

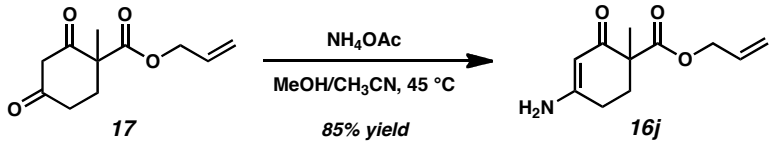
160.8, 136.5, 131.6, 129.0, 127.9, 127.5, 123.8, 1190, 66.1, 52.6, 50.8, 32.8, 27.3, 23.2, 20.2; IR (Neat Film NaCl) 3063, 3030, 2981, 2937, 2873, 1731, 1667, 1624, 1496, 1454, 1424, 1387, 1375, 1344, 1312, 1250, 1190, 1113, 1029, 986, 948, 882, 738 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{24}O_4N$ $[M+H]^+$: 342.1700, found 342.1705.



Enaminone 16i. Adapted from procedure by Buchwald.[30] Prepared from **20** in an analogous manner to **16h**. Purified by flash chromatography (SiO_2, 12 x 3 cm, 20→33→50% EtOAc in hexanes) to afford enaminone **16i** (220 mg, 0.702 mmol, 70% yield) as a pale yellow oil that solidified to a pale yellow amorphous solid upon standing at –20 °C; R_f = 0.10 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.83 – 7.74 (m, 2H), 7.56–7.47 (m, 1H), 7.47–7.40 (m, 2H), 6.70 (s, 1H), 5.88–5.75 (m, 1H), 5.25 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.55 (dq, *J* = 5.5, 1.5 Hz, 2H), 2.92–2.82 (m, 1H), 2.79–2.69 (m, 1H), 2.53 (dt, *J* = 13.7, 5.4 Hz, 1H), 1.99–1.87 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 172.5, 166.5, 155.6, 133.8, 132.7, 131.7, 128.9, 127.5, 118.4, 111.1, 65.8, 52.3, 32.0, 25.9, 20.5; IR (Neat Film NaCl) 3334, 2936, 1732, 1694, 1621, 1514, 1492, 1376, 1258, 1185, 1115, 1071, 1023, 931, 710 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{20}NO_4$ $[M+H]^+$: 314.1387, found 314.1381.



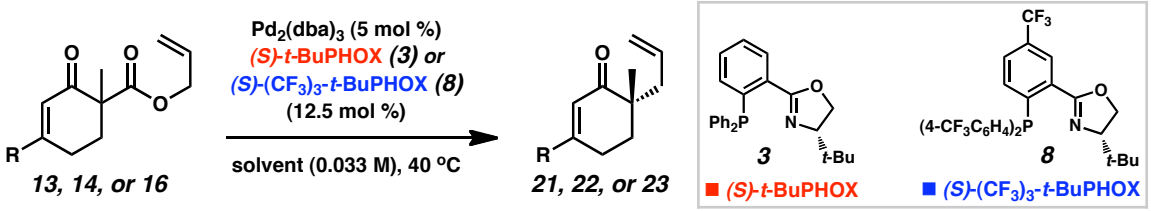
Enaminone 16e. Prepared from **16i** in an analogous manner to **16d**. Purified by flash chromatography (SiO_2, 15 x 3 cm, 20% acetone in hexanes) to afford enaminone **16e** (134 mg, 0.332 mmol, 60% yield) as a yellow oil; $R_f = 0.63$ (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.65–7.55 (m, 2H), 7.52–7.43 (m, 1H), 7.43–7.37 (m, 2H), 7.36–7.26 (m, 5H), 5.84 (s, 1H), 5.83–5.71 (m, 1H), 5.28–5.15 (m, 2H), 5.10–4.98 (m, 2H), 4.58–4.38 (m, 2H), 2.38–2.26 (m, 1H), 2.26–2.13 (m, 2H), 1.56 (s, 6H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9, 171.8, 161.8, 136.8, 136.0, 131.8, 131.6, 128.9, 128.8, 128.2, 127.9, 127.7, 127.7, 121.4, 118.5, 65.9, 52.8, 52.4, 32.6, 28.8, 20.2; IR (Neat Film NaCl) 2936, 1733, 1661, 1601, 1496, 1447, 1377, 1344, 1300, 1253, 1174, 1111, 974, 794, 724 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}NO_4$ $[M+H]^+$: 404.1856, found 404.1850.



Enaminone 16j. A flame-dried 50 mL round-bottom flask containing a stir bar was cycled into a glove box and loaded with ammonium acetate (185.3 mg, 2.40 mmol, 1.16 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, and charged with MeOH (1.5 mL). Dione **17** (437.5 mg, 2.08 mmol, 1.00 equiv) was transferred to the flask via cannula using MeOH (5 mL, total added = 6.5 mL, 0.32 M) and CH_3CN (6.5 mL, 0.32 M) rinses. The flask was lowered into a preheated oil bath (45

°C) and the reaction was heated for five days before TLC analysis indicated consumption of starting material. The reaction was cooled to room temperature and the contents were concentrated under reduced pressure. The resulting crude material was recrystallized twice with toluene to produce enaminone **16j** (369.0 mg, 1.76 mmol, 85% yield) as a white crystal; R_f = 0.18 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dddd, J = 17.2, 10.4, 5.5, 5.5 Hz, 1H), 5.29 (dq, J = 17.2, 1.6 Hz, 1H), 5.25 (d, J = 0.8 Hz, 1H), 5.20 (dq, J = 10.5, 1.4 Hz, 1H), 4.61 (dddd, J = 5.4, 3.9, 1.5, 1.5 Hz, 2H), 4.53 (broad s, 2H), 2.60–2.52 (m, 1H), 2.49 (ddd, J = 13.3, 5.8, 5.0 Hz, 1H), 2.35–2.28 (m, 1H), 1.93–1.86 (m, 1H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 173.3, 163.7, 132.1, 118.1, 99.9, 65.7, 51.6, 32.3, 26.0, 21.0; IR (Neat Film NaCl) 3338, 3189, 3064, 2983, 2934, 2873, 1735, 1654, 1551, 1437, 1383, 1358, 1291, 1253, 1216, 1194, 1175, 1103, 989, 930, 841, 824 cm^{-1}; HRMS (MM: ESI-APCI+) calc'd for $C_{11}H_{16}O_3N$ $[M+H]^+$: 210.1125, found 210.1119.

1.4.2.2.2 *General Procedure for Screening Reactions*



entry	substrate	R	product	ligand	Enantiomeric Excess (% ee)[b] THF	TBME	Toluene	2:1 Hex–Tol
1	*13a*	H	*21a*	*3*	87	88	87	87
2				*8*	85	86	88	85
3	*14a*	O*i*-Bu	*22a*	*3*	85	85	86	87
4				*8*	86	86	86	88
5	*16a*	NMe(Bn)	*23a*	*3*	61	60	55	52
6				*8*	79	78	84	83
7	*16b*	NPh(Bn)	*23b*	*3*	81	87	85	83
8				*8*	76	74	82	83
9	*16d*	NAc(Bn)	*23d*	*3*	89	90	88	88
10				*8*	83	85	88	86
11	*16e*	NBz(Bn)	*23e*	*3*	86	87	88	87
12				*8*	80	83	82	83
13	*16f*	NBoc(Bn)	*23f*	*3*	87	86	87	82
14				*8*	84	84	81	83
15	*16g*	NTs(Bn)	*23g*	*3*	84	83	83	82
16				*8*	82	83	83	83

[a] *Conditions*: enone **13a**, vinylogous ester **14a**, or enaminone **16a, b, d–g** (1.0 equiv), $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in solvent (0.033 M) at 40 °C. [b] Determined by GC, HPLC, or SFC analysis. Red = with *(S)*-(**3**) as ligand and blue = with *(S)*-(**8**) as ligand.

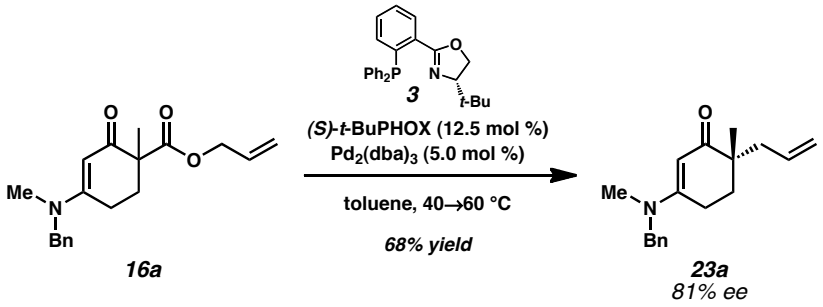
Enone 13a Screen Procedure. $Pd_2(dba)_3$ (2.4 mg, 0.00262 mmol, 0.05 equiv) and the appropriate PHOX ligand ((*S*)-*t*-BuPHOX (**3**): 2.5 mg, 0.00645 mmol, 0.125 equiv ***or*** (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**): 3.8 mg, 0.00643 mmol, 0.125 equiv) were added to an oven-dried 1 dram vial equipped with a magnetic stir bar. A separate oven-dried 1 dram vial was charged with enone **13a**[6] (10.0 mg, 0.0515 mmol, 1.00 equiv) and both vials were cycled into a nitrogen-filled glove box. The palladium/ligand vial was charged with

solvent (THF, TBME, toluene: 360 μL or 2:1 hexanes/toluene: 120 μL toluene and 340 μL hexanes) and stirred at ambient glove box temperature. After 30 min, enone **9a** was transferred to the reaction vial with several solvent rinses (THF, TBME, toluene: 3 x 400 μL, 1.56 mL total, 0.033 M or 2:1 hexanes/toluene: 400 μL toluene and 400 μL + 300 μL hexanes, 1.56 mL solvent total, 0.033 M). The vials were tightly sealed with a teflon lined cap and electrical tape, removed from the glove box, and lowered into a heating block set to 40 °C. After 2 days, the reaction were either loaded directly onto a column (toluene and 2:1 hexanes/toluene) or filtered through a celite plug and concentrated prior to chromatography (THF and TBME). All reactions were purified by flash column chromatography (SiO_2, ~22 x 1 cm, 2%→3% Et_2O in pentane), resuspended in Et_2O for analysis, and analyzed for enantiomeric excess with chiral GC. Characterization data for enone **21a** matches that previously reported.[6] As part of the screen, the yield was determined for enone **21a** with (*S*)-**8** in toluene (6.0 mg, 0.040 mmol, 78% yield).

Vinylogous Ester 14a and Enaminone Symyx Core Module Screen Procedure. All reagents were dispensed as solutions using a Symyx Core Module within a nitrogen-filled glovebox. Oven-dried half-dram vials were charged with a solution of the palladium source ($Pd_2(dba)_3$, 1.65 μmol, 0.05 equiv) in THF (400 μL). The palladium solutions were evaporated to dryness under reduced pressure using a Genevac centrifugal evaporator within the glovebox, and stirbars were added to the vials. The reaction vials were then charged with a solution of the PHOX ligand (4.13 μmol, 0.125 equiv) in the reaction solvent (300 μL) and stirred at 20 °C. After 30 min, a solution of vinylogous

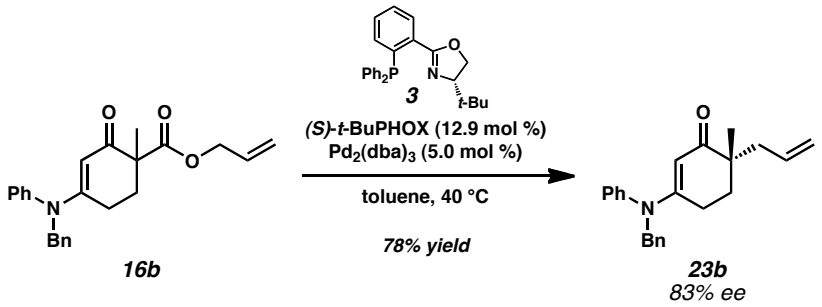
ester **14a** or the enaminone substrate (**16**, 33.0 μmol, 1.0 equiv) in the reaction solvent (700 μL) were added. The reaction vials were tightly capped and heated to the desired temperature (40 °C). The consumption of the starting material was observed by colorimetric change (from light yellow/green to red/orange) and after 5 days, the reactions were removed from the glovebox, filtered through a short silica gel plug (rinsing with EtOAc), concentrated under reduced pressure, resuspended in an appropriate solvent for analysis (HPLC: hexanes ***or*** SFC: MeOH), and analyzed for enantiomeric excess (see Methods for the Determination of Enantiomeric Excess). Characterization data for vinylogous ester **22a** matches that previously reported.[18c] Experimental procedures and characterization data for enaminones **23a**, **b**, **d**–**g** follows.

1.4.2.2.3 *Enaminone Allylic Alkylation Products*



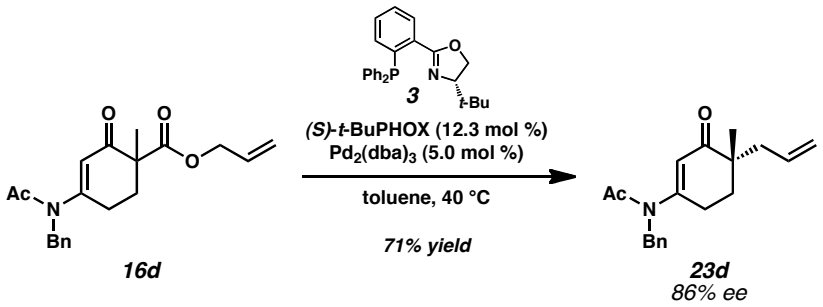
Enaminone 23a. $Pd_2(dba)_3$ (14.6 mg, 0.0159 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 15.5 mg, 0.0400 mmol, 12.5 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (2 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16a** (1 M in toluene, 320 μL, 0.320 mmol, 1.00 equiv) and additional toluene (7.35 mL, total added = 9.67 mL, 0.033 M) were added, producing a

green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 5 days, the temperature was raised to 60 °C and heated for an additional day before the reaction mixture transitioned back to a red/orange solution. The reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified twice by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→20%→30%→50% EtOAc in hexanes→ 100% EtOAc ***then*** SiO_2, 26.5 x 1.5 cm, 100% hexanes→20%→30%→40% EtOAc in hexanes) to afford enaminone **23a** (58.9 mg, 0.219 mmol, 68% yield) as a pale yellow oil; R_f = 0.12 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2H), 7.31–7.26 (m, 1H), 7.10 (d, J = 7.2 Hz, 2H), 5.84–5.74 (m, 1H), 5.17 (s, 1H), 5.07–5.00 (m, 2H), 4.51 (s, 2H), 2.95 (s, 3H), 2.58–2.44 (m, 2H), 2.38 (dddd, J = 13.7, 7.1, 1.2, 1.2 Hz, 1H), 2.23–2.18 (m, 1H), 1.93 (ddd, J = 13.2, 7.5, 5.5 Hz, 1H), 1.71 (ddd, J = 13.7, 6.9, 5.4 Hz, 1H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 163.7, 136.9, 135.2, 129.1, 127.7, 126.3, 117.5, 98.1, 55.0, 42.1, 41.8, 38.5, 32.8, 24.0, 22.6; IR (Neat Film NaCl) 3066, 3029, 2958, 2926, 2867, 1728, 1615, 1557, 1495, 1451, 1412, 1373, 1354, 1333, 1315, 1297, 1276, 1253, 1204, 1156, 1103, 1077, 1029, 1001, 924, 823, 792, 733 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{23}ON$ $[M+\bullet]^+$: 269.1780, found 269.1782; $[\alpha]_D^{25.0}$ –24.18 (c 1.04, $CHCl_3$, 81% ee); JASCO SFC conditions: 5% MeOH in CO_2, 5 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 10.45, minor = 9.60.



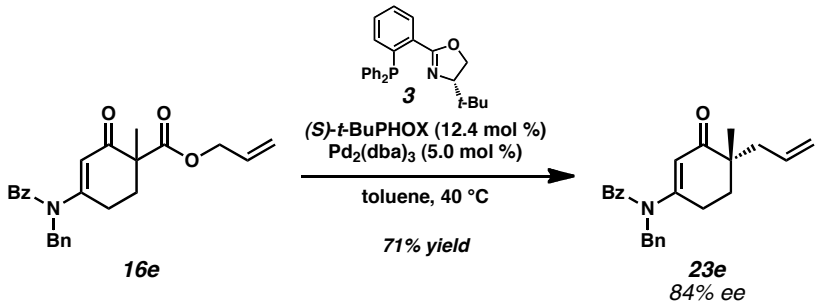
Enaminone 23b. $Pd_2(dba)_3$ (3.5 mg, 0.00382 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 3.8 mg, 0.00981 mmol, 12.9 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (0.5 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16b** (28.6 mg, 0.0762 mmol, 1.00 equiv) was transferred to the flask with several toluene rinses (1 x 0.81 mL + 2 x 0.5 mL, total added = 2.31 mL, 0.033 M), producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 4 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified twice by flash column chromatography (SiO_2, 19.5 x 1.5 cm, 100% hexanes→50% EtOAc in hexanes→100% EtOAc ***then*** SiO_2, 23.5 x 1 cm, 100% hexanes→10%→20%→30%→40% EtOAc in hexanes) to afford enaminone **23b** (19.7 mg, 0.0594 mmol, 78% yield) as a frosty colorless oil; R_f = 0.63 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2H), 7.33–7.29 (m, 2H), 7.29–7.22 (m, 2H), 7.22–7.18 (m, 2H), 7.15–7.11 (m, 2H), 5.76 (dddd, J = 15.8, 11.3, 7.8, 7.0 Hz, 1H), 5.29 (s, 1H), 5.05–5.00 (m, 2H), 4.83 (s, 2H), 2.38 (dddd, J = 13.8, 7.1, 1.3, 1.3 Hz, 1H), 2.35–2.31 (m, 2H), 2.19 (dddd, J = 13.7, 7.8, 1.1, 1.1 Hz, 1H),

1.90–1.83 (m, 1H), 1.65 (ddd, J = 13.5, 6.5, 5.6 Hz, 1H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 163.3, 144.6, 136.7, 135.0, 129.8, 128.8, 128.0, 127.6, 127.5, 127.0, 117.6, 100.5, 56.7, 42.2, 42.0, 33.0, 25.5, 22.6; IR (Neat Film NaCl) 3063, 3031, 2959, 2926, 2863, 1622, 1563, 1494, 1453, 1426, 1404, 1374, 1351, 1329, 1275, 1204, 1156, 1078, 1060, 1028, 1002, 911, 830, 730 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{26}ON$ $[M+H]^+$: 332.2009, found 332.1999; $[\alpha]_D^{25.0}$ –29.79 (c 1.91, $CHCl_3$, 83% ee); JASCO SFC conditions: 5% MeOH in CO_2, 5 mL/min, Chiralpak AS-H column, λ = 254 nm, t_R (min): major = 8.60, minor = 6.48.



Enaminone 23d. $Pd_2(dba)_3$ (2.6 mg, 0.00284 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 2.7 mg, 0.00697 mmol, 12.3 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (0.51 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16d** (19.3 mg, 0.0565 mmol, 1.00 equiv) was transferred to the flask with several toluene rinses (4 x 0.3 mL, total added = 1.71 mL, 0.033 M), producing a yellow solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a

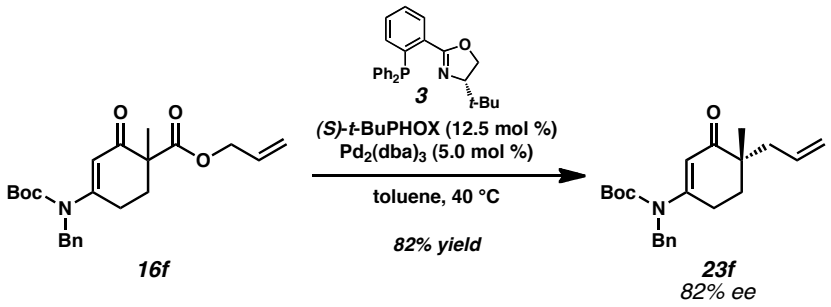
silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 19.5 x 1.5 cm, 5%→10%→20%→30% EtOAc in hexanes) to afford enaminone **23d** (12.0 mg, 0.0404 mmol, 71% yield) as a yellow oil; R_f = 0.46 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (ddt, J = 8.1, 6.7, 1.2 Hz, 2H), 7.30–7.23 (m, 1H), 7.19 (ddt, J = 7.3, 1.4, 0.7 Hz, 2H), 5.68 (t, J = 1.3 Hz, 1H), 5.66 (ddt, J = 16.9, 10.1, 7.3 Hz, 1H), 5.05 (ddt, J = 10.1, 1.9, 0.9 Hz, 1H), 4.99 (ddt, J = 17.0, 2.1, 1.4 Hz, 1H), 4.81 (s, 2H), 2.50–2.39 (m, 2H), 2.21 (ddt, J = 13.8, 7.3, 1.2 Hz, 1H), 2.17 (s, 3H), 2.10 (ddt, J = 13.8, 7.5, 1.1 Hz, 1H), 1.87 (dt, J = 13.8, 5.9 Hz, 1H), 1.69 (ddd, J = 13.8, 6.6, 5.7 Hz, 1H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 169.7, 160.1, 136.6, 133.6, 128.9, 127.9, 127.7, 123.8, 118.6, 50.9, 43.6, 40.8, 32.6, 27.1, 23.2, 21.5; IR (Neat Film NaCl) 3066, 2926, 2854, 1663, 1624, 1496, 1453, 1387, 1371, 1189, 991, 916 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{24}NO_2$ $[M+H]^+$: 298.1807, found 298.1794; $[\alpha]_D^{25.0}$ –14.12 (c 1.20, $CHCl_3$, 86% ee); Thar SFC conditions: 5% MeOH in CO_2, 3 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 8.45, minor = 10.35.



Enaminone 23e. $Pd_2(dba)_3$ (4.6 mg, 0.00502 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 4.8 mg, 0.0124 mmol, 12.4 mol %) were added to an oven-dried scintillation vial

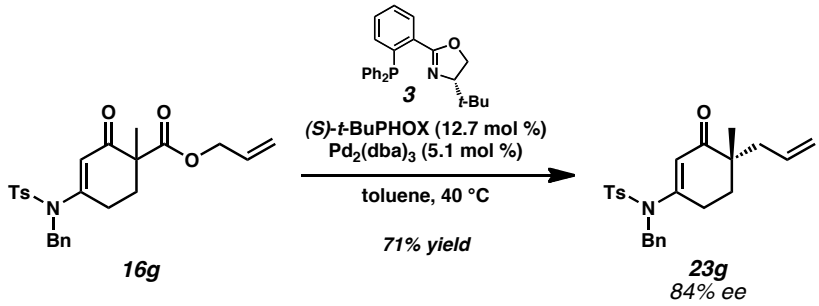
equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (0.93 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16e** (1 M in toluene, 100 μL, 0.100 mmol, 1.00 equiv) was transferred to the flask with more toluene (1 mL, total added including enaminone solution = 3.03 mL, 0.033 M), producing a yellow/orange solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 19.5 x 1.5 cm, 5%→10%→15% EtOAc in hexanes) to afford enaminone **23e** (26.3 mg, 0.0713 mmol, 71% yield, 95% purity) as a yellow oil; $R_f = 0.57$ (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.59 (m, 2H), 7.50–7.43 (m, 1H), 7.39 (ddt, J = 8.2, 6.6, 1.1 Hz, 2H), 7.35–7.29 (m, 4H), 7.29–7.25 (m, 1H), 5.74 (t, J = 1.1 Hz, 1H), 5.54 (ddt, J = 17.3, 10.1, 7.4 Hz, 1H), 5.09 (d, J = 15.3 Hz, 1H), 5.00 (d, J = 15.3 Hz, 1H), 4.98 (dm, J = 9.9 Hz, 1H), 4.86 (dm, J = 17.0 Hz, 1H), 2.11–2.08 (m, 2H), 2.03 (dd, J = 14.2, 7.9 Hz, 1H), 1.95 (ddt, J = 13.8, 7.3, 1.2 Hz, 1H), 1.59 (ddd, J = 13.7, 6.5, 5.4 Hz, 1H), 1.41 (ddd, J = 13.4, 6.8, 5.3 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 170.8, 160.9, 136.8, 136.2, 133.6, 131.6, 128.9, 128.7, 128.1, 128.0, 127.9, 122.3, 118.4, 52.5, 43.3, 40.6, 32.4, 28.4, 21.3; IR (Neat Film NaCl) 3063, 3030, 2961, 2928, 2855, 1655, 1610, 1496, 1447, 1384, 1374, 1347, 1324, 1273, 1189, 1140, 1076, 1028, 1001, 974, 919, 792 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{24}H_{26}NO_2$ $[M+H]^+$: 360.1964, found 360.1956; $[\alpha]_D^{25.0}$ –26.61 (c 1.87, $CHCl_3$, 84% ee); Thar SFC

conditions: 7% MeOH in CO_2, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 18.14, minor = 20.28.



Enaminone 16f. $Pd_2(dba)_3$ (11.5 mg, 0.0126 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 12.1 mg, 0.0312 mmol, 12.5 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (2 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16f** (1 M in toluene, 250 μL, 0.250 mmol, 1.00 equiv) and additional toluene (6.34 mL, total added = 7.59 mL, 0.033 M) were added, producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 28 x 3 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford enaminone **23f** (72.6 mg, 0.204 mmol, 82% yield) as a pale yellow oil; R_f = 0.65 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.26–7.22 (m, 1H), 7.17–7.14 (m, 2H), 5.69 (dddd, J = 16.8, 10.2, 7.4, 7.4 Hz, 1H), 5.63 (t, J = 0.9 Hz, 1H), 5.07–4.99 (m, 2H), 4.78 (s, 2H), 2.75 (tm,

J = 6.1 Hz, 2H), 2.29 (dddd, J = 13.7, 7.3, 1.2, 1.2 Hz, 1H), 2.13 (dddd, J = 13.7, 7.5, 1.2, 1.2 Hz, 1H), 1.90–1.84 (m, 1H), 1.71–1.65 (m, 1H), 1.43 (s, 9H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 161.6, 153.0, 137.4, 134.1, 128.8, 127.4, 126.4, 118.2, 115.4, 82.6, 52.9, 43.2, 41.2, 33.5, 28.2, 27.2, 21.9; IR (Neat Film NaCl) 3066, 3031, 3004, 2976, 2931, 2868, 1716, 1656, 1598, 1497, 1455, 1428, 1382, 1368, 1350, 1326, 1302, 1243, 1209, 1192, 1153, 1076, 1030, 998, 946, 916, 858, 779, 767, 734 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{30}O_3N$ $[M+H]^+$: 356.2229, found 356.2220; $[\alpha]_D^{25.0}$ –23.61 (c 0.92, $CHCl_3$, 82% ee); JASCO SFC conditions: 7% MeOH in CO_2, 5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 4.04, minor = 2.20.

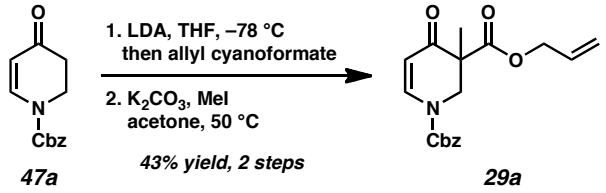


Enaminone 23g. $Pd_2(dba)_3$ (10.2 mg, 0.0111 mmol, 5.1 mol %) and (*S*)-*t*-BuPHOX (**3**, 10.8 mg, 0.0279 mmol, 12.7 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (2 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16g** (1 M in toluene, 220 μL, 0.220 mmol, 1.00 equiv) and additional toluene (5.46 mL, total added = 6.68 mL, 0.033 M) were added, producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture

transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27 x 2 cm, 100% hexanes→5%→10%→15% EtOAc in hexanes) to afford enaminone **23g** (64.1 mg, 0.157 mmol, 71% yield) as a pale yellow oil; R_f = 0.55 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dm, J = 8.3 Hz, 2H), 7.35 (dm, J = 8.6 Hz, 2H), 7.33–7.26 (m, 3H), 7.25–7.22 (m, 2H), 5.60–5.50 (m, 2H), 4.98 (dm, J = 10.2 Hz, 1H), 4.86 (dm, J = 17.0 Hz, 1H), 4.74 (d, J = 15.0 Hz, 1H), 4.66 (d, J = 15.0 Hz, 1H), 2.56–2.44 (m, 2H), 2.46 (s, 3H), 1.99–1.86 (m, 2H), 1.70 (ddd, J = 13.9, 6.6, 5.3 Hz, 1H), 1.55 (ddd, J = 13.9, 7.2, 5.5 Hz, 1H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 157.74, 144.7, 135.4, 135.3, 133.7, 130.1, 128.9, 128.1, 127.9, 127.5, 120.7, 118.3, 53.1, 43.2, 40.6, 32.2, 27.9, 21.8, 21.3; IR (Neat Film NaCl) 3066, 3027, 2963, 2928, 2868, 1663, 1654, 1597, 1496, 1453, 1424, 1355, 1306, 1164, 1089, 1055, 1028, 1001, 912, 859, 814, 745 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{28}O_3NS$ $[M+H]^+$: 410.1784, found 410.1792; $[\alpha]_D^{25.0}$ –33.05 (c 0.37, $CHCl_3$, 84% ee); JASCO SFC conditions: 10% MeOH, 5 mL/min, AD-H column, λ = 210 nm, t_R (min): major = 5.60, minor = 4.73.

1.4.2.3 Preparation of 2,3-Dihydropyridin-4-ones

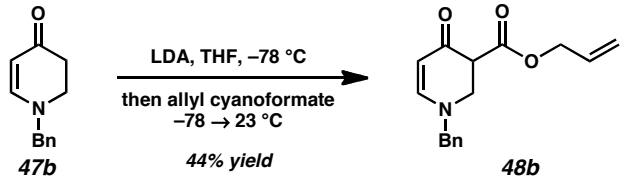
1.1.1.1.4 *2,3-Dihydropyridin-4-one Allylic Alkylation Precursors*



2,3-Dihydropyridin-4-one 29a. A 100 mL round-bottom flask equipped with a magnetic stir bar was charged with diisopropyl amine (442 µL, 3.01 mmol, 1.20 equiv) and THF (28 mL). The flask was cooled to –78 °C bath (dry ice/IPA) and *n*-BuLi (1.30 mL, 3.01 mmol, 2.32 M in hexanes, 1.20 equiv) was added. The reaction was allowed to warm to 0 °C over 1 h. The solution was cooled back to –78 °C and added dropwise to a solution of 2,3-dihydropyridin-4-one **47a**[37] (580 mg, 2.51 mmol, 1.0 equiv) in THF (40 mL) at –78 °C using positive pressure cannulation. The reaction was stirred for 1 h at this temperature before allyl cyanoformate (300 µL, 2.88 mmol, 1.15 equiv) was added dropwise. The flask was removed from the bath, allowed to warm to room temperature slowly, and stirred overnight. The reaction was quenched with water and sat. NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduce pressure. The resulting yellow oil was purified by flash-chromatography (2:1 Et_2O/hexanes).

The yellow oil was transferred to an argon filled 25 mL Schlenk tube equipped with a magnetic stir bar using several acetone rinses (3 x 2 mL). K_2CO_3 (252 mg, 1.83 mmol, 2.0 equiv) and methyl iodide (115 µL, 1.84 mmol, 2.02 equiv) were added to the

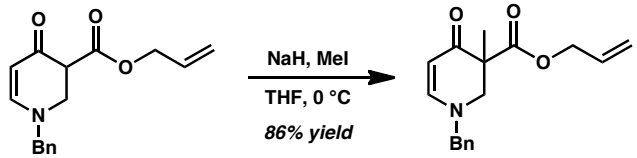
reaction. The resulting suspension was heated to 50 °C and vigorously stirred for 14 h. Upon completion, the reaction was allowed to cool to room temperature and filtered through a plug of celite. The resulting yellow solution was concentrated under reduced pressure and purified by flash-chromatography (1:1 Et_2O/hexanes) to afford 2,3-Dihydropyridin-4-one **29a** (210 mg, 0.64 mmol, 43% yield over two steps) as a yellow oil; R_f = 0.38 (1:1 Et_2O/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (br s, J = 22.5 Hz, 1H), 7.45–7.31 (m, 5H), 5.82 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.37 (br s, 1H), 5.27 (s, 2H), 5.26 (dq, J = 17.1, 1.5 Hz, 1H), 5.20 (dq, J = 10.5, 1.3 Hz, 1H), 4.64 (dd, J = 13.5, 0.9 Hz, 1H), 4.59 (dt, J = 5.6, 1.5 Hz, 2H), 3.63 (d, J = 13.5 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ190.9, 170.1, 152.5, 142.7, 134.8, 131.3, 128.8, 128.7, 128.4, 118.6, 106.2, 69.2, 66.1, 51.6, 50.5, 17.9; IR (Neat Film, NaCl) 3076, 3034, 2965, 2929, 2360, 2922, 1729, 1668, 1605, 1498, 1456, 1418, 1393, 1344, 1302, 1205, 1157, 1101, 1029, 966, 917, 814, 763 cm^{-1}; HRMS (MM: ESI/APCI+) *m/z* calc'd for $C_{18}H_{20}NO_5$ $[M+H]^+$: 330.1335, found 330.1335.



47b *48b*

2,3-Dihydropyridin-4-one 48b. To a flame-dried 50 mL Schlenk round-bottom flask equipped with a magnetic stir bar was added 2,3-dihydropyridin-4-one **47b**[38] (162.0 mg, 0.87 mmol) and THF (10 mL). The solution was cooled to –78 °C and LDA (0.1 M in THF, 9.10 mL, 0.91 mmol, 1.05 equiv) was added dropwise by syringe. After 1 h at –78 °C, allyl cyanoformate (105.2 mg, 0.96 mmol, 1.10 equiv) was added, and the reaction

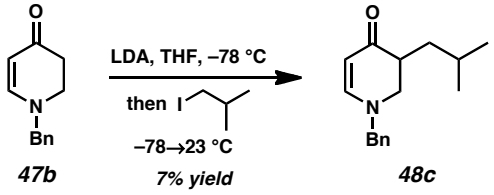
was stirred for another 3 h and then quenched with a sat. NH_4Cl sol. The reaction was transferred to a separatory funnel where the aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL). The combined organics were washed with brine, dried over $MgSO_4$, fitered, and concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography (SiO_2, 10 x 2.5 cm, 30% EtOAc → 50% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **48b** (104.8 mg, 0.38 mmol, 44% yield) as a yellow oil; R_f = 0.30 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.31 (m, 3H), 7.28–7.23 (m, 2H), 7.17 (d, *J* = 7.5 Hz, 1H), 5.87 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.22 (dq, *J* = 10.4, 1.3 Hz, 1H), 5.06 (d, *J* = 7.5 Hz, 1H), 4.69–4.55 (m, 2H), 4.40 (d, *J* = 2.5 Hz, 2H), 3.76 (dd, *J* = 13.3, 8.7 Hz, 1H), 3.51 (dd, *J* = 13.3, 5.9 Hz, 1H), 3.40 (dd, *J* = 8.7, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2, 168.8, 153.6, 135.1, 131.6, 129.1, 128.5, 127.8, 118.6, 97.7, 66.0, 60.0, 50.5, 48.4; IR (Neat Film NaCl) 3029, 2935, 2853, 1732, 1641, 1588, 1494, 1455, 1393, 1361, 1321, 1204, 1154, 1078, 1028, 991, 967, 935, 78, 731 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{18}NO_3$ $[M+H]^+$: 272.1287, found 272.1314.



48b *29b*

2,3-Dihydropyridin-4-one 29b. To a flame-dried 25 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box and loaded with sodium hydride (9.3 mg, 0.39 mmol, 1.00 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, charged with THF (3 mL), and cooled to 0 °C. A solution of 2,3-

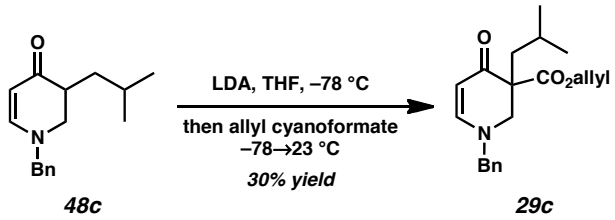
dihydropyridin-4-one **48b** (104.2 mg, 0.39 mmol, 1.00 equiv) was added by syringe and the mixture was stirred at 0 °C for 30 min. The reaction was quenched with water, transferred to a separatory funnel, and extracted four times with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 10 x 2.5 cm, 30% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **29b** (95.9 mg, 0.34 mmol, 86% yield) as a colorless oil; R_f = 0.40 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.30 (m, 3H), 7.25–7.20 (m, 2H), 7.13 (d, *J* = 7.4 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.8, 5.5 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.19 (dq, *J* = 10.5, 1.3 Hz, 1H), 5.01 (d, *J* = 7.4 Hz, 1H), 4.56 (qdt, *J* = 13.4, 5.5, 1.5 Hz, 2H), 4.46–4.30 (m, 2H), 3.78 (d, *J* = 13.2 Hz, 1H), 3.15 (d, *J* = 13.3 Hz, 1H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 171.7, 152.8, 135.2, 131.8, 129.1, 128.5, 128.1, 118.2, 97.1, 65.9, 60.1, 55.1, 51.4, 18.6; IR (Neat Film NaCl) 3029, 2979, 2934, 2871, 1732, 1642, 1592, 1494, 1455, 1393, 1372, 1359, 1343, 1295, 1223, 1166, 1115, 1028, 975, 937, 792, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1443, found 286.1480.



47b *7% yield* *48c*

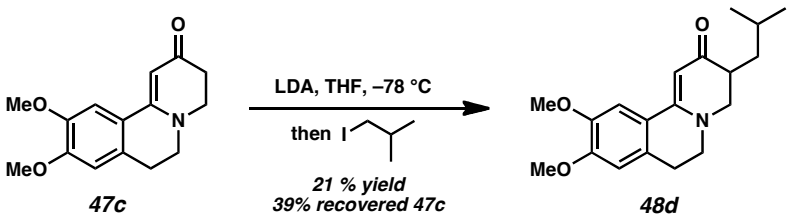
2,3-Dihydropyridin-4-one 48c. To a flame-dried 100 mL Schlenk round-bottom flask equipped with a magnetic stir bar was added 2,3-dihydropyridin-4-one **47b**[38] (0.68 g, 3.63 mmol) and THF (30 mL). The solution was cooled to –78 °C and LDA (19.0 mL, 3.80

mmol, 1.05 equiv, 0.2 M in THF) was added dropwise by syringe. After 1 h at –78 °C, 1-iodo-2-methylpropane (0.87 g, 4.73 mmol, 1.30 equiv) was added, and the reaction was stirred for another 1 h at –78 °C, brought to room temperature, and stirred overnight. The reaction was quenched with a sat. NH_4Cl sol., transferred to a separatory funnel, and extracted with CH_2Cl_2 (50 mL x 3). The combined organics were washed with brine, dried over $MgSO_4$, fitered, and concentrated. The crude mixture was purified by flash chromatography (SiO_2, 10 x 3 cm, 30% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **48c** (58.2 mg, 0.24 mmol, 7% yield) as a yellow oil; R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.32 (m, 3H), 7.29–7.25 (m, 2H), 7.12 (d, J = 7.4 Hz, 1H), 4.96 (d, J = 7.4 Hz, 1H), 4.43–4.28 (m, 2H), 3.38 (dd, J = 13.0, 5.4 Hz, 1H), 3.08 (dd, J = 13.0, 7.7 Hz, 1H), 2.29 (ddt, J = 10.1, 7.6, 5.2 Hz, 1H), 1.56 (ddd, J = 14.0, 9.3, 5.0 Hz, 1H), 1.37 (dpd, J = 9.3, 6.6, 5.2, 1H), 1.18 (ddd, J = 13.7, 9.6, 5.3 Hz, 1H), 0.82 (d, J = 6.5 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 152.8, 135.8, 128.9, 128.3, 127.8, 97.7, 60.0, 50.4, 42.0, 37.5, 25.0, 23.3, 21.4; IR (Neat Film NaCl) 3029, 2954, 2868, 1633, 1593, 1494, 1463, 1455, 1385, 1361, 1302, 1210, 1161, 1077, 778, 730 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{22}NO$ $[M+H]^+$: 244.1701, found 244.1707.

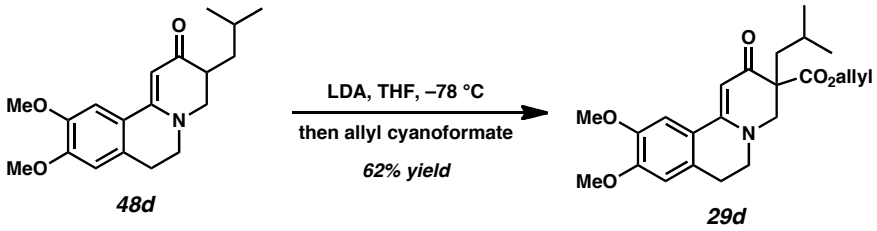


48c ***29c***

2,3-Dihydropyridin-4-one 29c. To a flame-dried 25 mL Schlenk tube equipped with a magnetic stir bar was added 2,3-dihydropyridin-4-one **48c** (50.5 mg, 0.21 mmol) and THF (5 mL). After the solution was cooled to -78 °C, LDA (2.2 mL, 0.22 mmol, 1.06 equiv, 0.1 M in THF) was added dropwise by syringe. The mixture was stirred for 1 h at -78 °C and allyl cyanoformate (26.4 mg, 0.24 mmol, 1.20 equiv) was added. The reaction was stirred for another 3 h and quenched with saturated NH_4Cl aqueous. The aqueous layer was extracted with CH_2Cl_2 (30 mL x 4) and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash chromatography (SiO_2, 10 x 1 cm, 30% EtOAc in hexanes) to afford **29c** (19.8 mg, 0.06 mmol, 30% yield) as a yellow oil; R_f = 0.30 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.31 (m, 3H), 7.29–7.19 (m, 2H), 7.07 (d, *J* = 7.4 Hz, 1H), 5.86 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.96 (d, *J* = 7.3 Hz, 1H), 4.67–4.51 (m, 2H), 4.43 (s, 2H), 3.82 (d, *J* = 13.4 Hz, 1H), 3.27 (d, *J* = 13.4 Hz, 1H), 2.03 (dd, *J* = 14.2, 7.1 Hz, 1H), 1.64–1.45 (m, 2H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ187.7, 170.9, 152.2, 135.1, 131.7, 129.0, 128.1, 118.4, 96.7, 65.8, 60.1, 54.4, 52.6, 40.4, 24.6, 24.3, 23.2; IR (Neat Film NaCl) 3029, 2957, 2870, 1729, 1644, 1593, 1455, 1360, 1267, 1215, 1159, 1132, 1077, 1029, 971, 778, 735 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{26}NO_3$ $[M+H]^+$: 328.1913, found 328.1947.



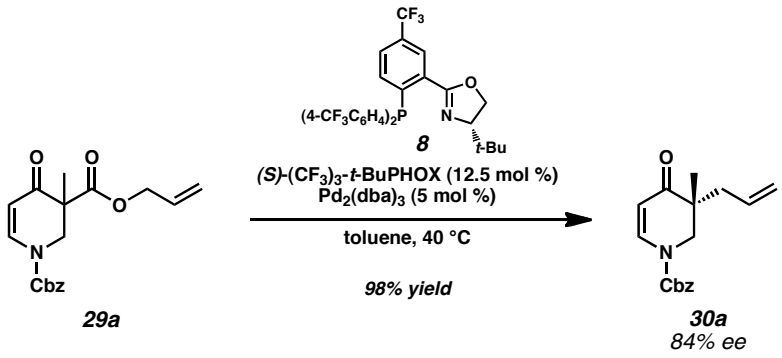
2,3-Dihydropyridin-4-one 48d. To a cooled (–78 °C) solution of **47c**[39] (0.67 g, 2.6 mmol, 1 equiv) in THF (25 mL) was added LDA (30 mL, 0.1 M, in THF, 30 mmol, 1.15 equiv) dropwise over 10 min. The reaction was stirred for 1 h before 1-iodo-2-methylpropane (0.57 g, 3.1 mmol, 1.20 equiv) was added dropwise. After 2 h, the reaction was brought to room temperature and stirred overnight. The reaction was quenched with sat. NH_4Cl sol. and transferred to a separatory funnel where the aqueous phase was extracted four times with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture purified by flash column chromatography (SiO_2, 15 x 3 cm, 50% EtOAc in hexanes→100% EtOAc) to afford recovered **47c** (0.26 g, 1.01 mmol, 39% recovered) and also **48d** (0.17 g, 0.54 mmol, 21% yield) as a yellow solid; R_f = 0.20 (50% EtOAc in hexanes). Spectral data matches that reported previously.[47] NMR data is included to assist the reader. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.65 (s, 1H), 5.62 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.64 (dd, J = 12.5, 5.3 Hz, 1H), 3.45–3.24 (m, 3H), 2.94 (td, J = 6.3, 3.5 Hz, 2H), 2.51–2.35 (m, 1H), 1.80–1.59 (m, 2H), 1.36–1.19 (m, 1H), 0.96 (d, J = 6.2 Hz, 3H), 0.91 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 156.6, 151.5, 148.1, 129.0, 120.9, 110.5, 108.4, 94.4, 56.1, 55.9, 49.2, 42.1, 37.6, 28.6, 25.6, 23.6, 21.9.



2,3-Dihydropyridin-4-one 29d. A solution of **48d** (149.1 mg, 0.47 mmol in 15 mol of THF) was cooled to –78 °C and LDA (5.2 mL, 0.1 M in THF, 0.52 mmol, 1.10 equiv) was added dropwise. The reaction was stirred for 1 h before allyl cyanoformate (60.2 mg, 0.54 mmol, 1.15 equiv) was added dropwise. After 12 h, the reaction was quenched with sat. NH_4Cl sol. and allowed to warm to room temperature. The reaction contents were transferred to a separatory funnel where the aqueous phase was extracted four times with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography (SiO_2, 15 x 3 cm, 50% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **29d** (116.0 mg, 0.29 mmol, 62% yield) as a yellow solid; R_f = 0.40 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 1H), 6.66 (s, 1H), 5.87 (ddt, J = 17.2, 10.3, 5.6 Hz, 1H), 5.59 (s, 1H), 5.30 (dq, J = 17.2, 1.6 Hz, 1H), 5.17 (dq, J = 10.4, 1.3 Hz, 1H), 4.61 (ddt, J = 5.6, 2.7, 1.4 Hz, 2H), 4.05 (d, J = 13.0 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.62 (d, J = 13.1 Hz, 1H), 3.55 (ddd, J = 12.1, 8.1, 5.7 Hz, 1H), 3.43 (ddd, J = 12.2, 6.9, 5.4 Hz, 1H), 3.00–2.77 (m, 2H), 2.23–2.06 (m, 1H), 1.79–1.60 (m, 2H), 0.96 (d, J = 6.2 Hz, 3H), 0.90 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 171.0, 155.7, 151.6, 148.0, 131.8, 129.0, 120.5, 118.3, 110.3, 108.4, 92.8, 65.7, 56.5, 56.0, 56.0, 54.5, 48.6, 40.4, 28.3, 25.0, 24.4, 23.5; IR (Neat Film NaCl) 2955, 1720, 1625, 1583, 1544, 1495, 1343, 1237, 1211, 1167, 11523, 1120, 1016

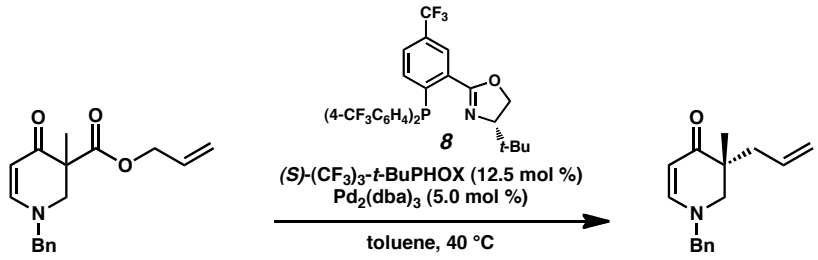
cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2124, found 400.2110.

1.4.2.3.5 *2,3-Dihydropyridin-4-one Allylic Alkylation Products*



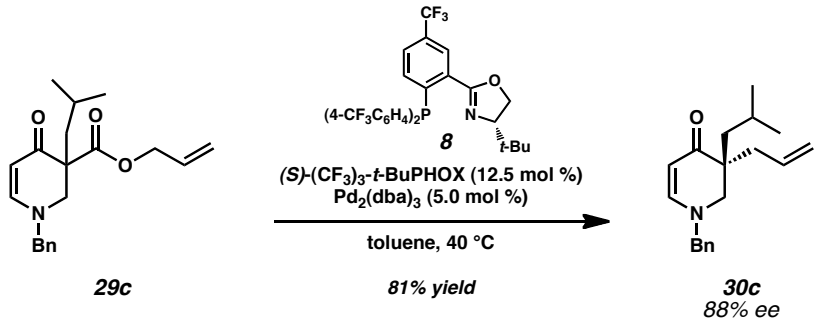
2,3-Dihydropyridin-4-one 30a. 2,3-Dihydropyridin-4-one **29a** (27.6 mg, 0.084 mmol, 1.0 equiv) was preloaded in a 1 dram vial and cycled into a glove box. A separate 1 dram vial was loaded with (S)-$(CF_3)_3$-*t*-Bu-PHOX (**8**, 4.1 mg, 10.5 µmol, 0.125 equiv), $Pd_2(dba)_3$ (3.9 mg, 4.20 µmol, 0.05 equiv), and a magnetic stir-bar. Toluene (1.6 mL) was added and the black suspension was stirred at 30 °C in a heating block for 30 min. 2,3-Dihydropyridin-4-one **29a** was dissolved in 1 mL of toluene and added to the orange catalyst solution, causing an immediate color change to olive green. The vial was capped with a Teflon screw cap and the reaction was stirred for 14 h at 40 °C in the glove box. Upon completion of the reaction, the vial was allowed to cool to room temperature and removed from the glove box. The reaction was concentrated under reduced pressure and the resulting brown oil was purified by flash-chromatography (1:1 Et_2O/hexanes) to afford 2,3-dihydropyridin-4-one **30a** (23.7 mg, 0.083 mmol, 98%) as a colorless oil; R_f = 0.73 (1:1 Et_2O/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.42–7.36 (m, 5H), 5.69 (td, J = 17.3, 7.5 Hz, 1H), 5.27 (d, J = 2.7 Hz, 3H), 5.05 (dd, J = 29.7, 13.4 Hz, 2H),

3.91 (d, J = 13.4 Hz, 1H), 3.58 (d, J = 11.8 Hz, 1H), 2.22 (ddd, J = 46.4, 13.8, 7.5 Hz, 2H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ198.3, 152.7, 141.7, 135.0, 132.6, 128.8, 128.7, 128.4, 119.2, 106.4, 69.1, 51.4, 43.4, 39.4, 19.5; IR (Neat Film, NaCl) 2922, 1728, 1673, 1602, 1498, 1453, 1416, 1381, 1342, 1305, 1232, 1200, 1144, 1119, 1088, 956, 913, 813, 761 cm^{-1}; HRMS (MM: ESI/APCI+) *m/z* calc'd for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1443, found 286.1438; $[\alpha]_D^{25.0}$ +9.88 (*c* 1.15, $CHCl_3$, 84% ee); Thar SFC conditions: 10% MeOH in CO_2, 3 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 2.80, minor = 3.13.



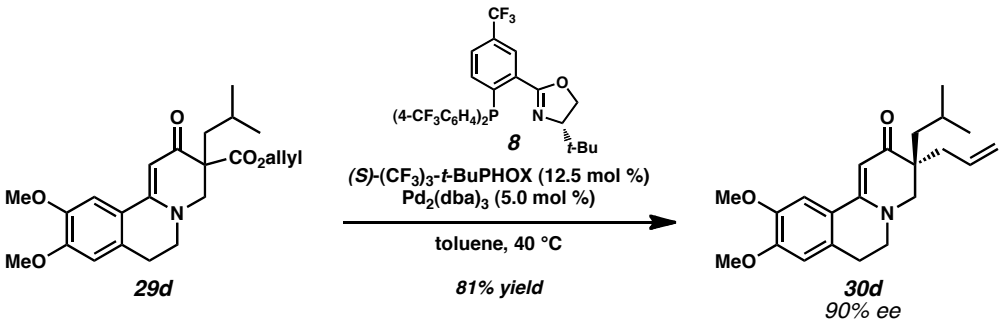
2,3-Dihydropyridin-4-one 30b. In a glove box, $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 3.7 mg, 0.00625 mmol, 12.5 mol %) were added to a scintillation vial equipped with a stir bar. The vial was charged with toluene (0.5 mL) and heated at 40 °C for 30 min. 2,3-Dihydropyridin-4-one **29b** (14.3 mg, 0.050 mmol, 1.00 equiv) and additional toluene (1.0 mL, total added = 1.5 mL, 0.033 M) were added, producing a green solution. The vial was sealed and stirred at 40 °C until the starting material was fully converted, determined by LCMS. The reaction was filtered through a celite pad, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 5 x 1 cm, 30% EtOAc in hexanes) to afford

2,3-dihydropyridin-4-one **30b** (11.3 mg, 0.047 mmol, 94% yield) as a yellow oil; R_f = 0.30 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.25 (m, 3H), 7.24–7.14 (m, 2H), 7.03 (d, *J* = 7.4 Hz, 1H), 5.54 (ddt, *J* = 17.4, 10.1, 7.4 Hz, 1H), 4.94 (ddt, *J* = 9.9, 1.9, 0.9 Hz, 1H), 4.91–4.81 (m, 2H), 4.27 (d, *J* = 3.1 Hz, 2H), 3.07 (d, *J* = 13.0 Hz, 1H), 2.90 (d, *J* = 13.0 Hz, 1H), 2.22–1.97 (m, 2H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ196.5, 152.3, 135.6, 133.6, 129.0, 129.0, 129.0, 128.3, 128.0, 118.3, 96.9, 60.1, 55.9, 42.7, 39.7, 20.1, 20.0; IR (Neat Film NaCl) 3067, 3029, 2962, 2926, 1634, 1593, 1455, 1359, 1321, 1204, 1172, 1076, 1001, 916, 795 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{20}NO$ $[M+H]^+$: 242.1545, found 242.1553; $[\alpha]_D^{25.0}$ +86.46 (c 1.16, $CHCl_3$, 86% ee); HPLC conditions: 10% IPA in hexanes, 1 mL/min, Chiralcel OJ column, λ = 210 nm, t_R (min): major = 18.77, minor = 21.21.



2,3-Dihydropyridin-4-one 30c. In a glove box, $Pd_2(dba)_3$ (1.4 mg, 0.0015 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 2.2 mg, 0.00375 mmol, 12.5 mol %) were added to a scintillation vial equipped with a stir bar. The vial was charged with toluene (0.5 mL) and heated at 40 °C for 30 min. 2,3-Dihydropyridin-4-one **29c** (9.8 mg, 0.030 mmol, 1.00 equiv) and additional toluene (0.5 mL, total added = 1.0 mL, 0.030 M) were added, producing a green solution. The vial was sealed and stirred at 40 °C until the starting

material was fully converted, determined by TLC. The reaction was filtered through a celite pad, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 5 x 1 cm, 30% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **30c** (6.9 mg, 0.024 mmol, 81% yield) as a yellow oil; R_f = 0.40 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.32 (m, 3H), 7.29–7.22 (m, 2H), 7.05 (d, *J* = 7.4 Hz, 1H), 5.62 (dddd, *J* = 17.1, 10.1, 7.8, 7.0 Hz, 1H), 5.00 (ddt, *J* = 10.1, 2.1, 1.0 Hz, 1H), 4.97–4.91 (m, 2H), 4.33 (s, 2H), 3.13 (d, *J* = 3.2 Hz, 2H), 2.34–2.24 (m, 1H), 2.16 (ddt, *J* = 14.1, 7.8, 1.1 Hz, 1H), 1.61 (qd, *J* = 6.7, 5.6 Hz, 1H), 1.47 (dd, *J* = 14.2, 6.3 Hz, 1H), 1.33 (dd, *J* = 14.2, 5.5 Hz, 1H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 152.4, 135.7, 133.7, 129.1, 128.5, 128.1, 118.4, 97.1, 60.2, 56.0, 42.8, 39.8, 20.2.; IR (Neat Film NaCl) 3072, 3029, 2954, 2867, 1633, 1593, 1494, 1455, 1385, 1361, 1296, 1205, 1173, 1105, 1076, 1028, 998, 793, 736 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{26}NO$ $[M+H]^+$: 284.2014, found 284.2023; $[\alpha]_D^{25.0}$ +50.23 (c 0.65, $CHCl_3$, 88% ee); HPLC conditions: 7% IPA in hexanes, 1 mL/min, Chiralcel OJ column, λ = 210 nm, t_R (min): major = 11.44, minor = 14.80.

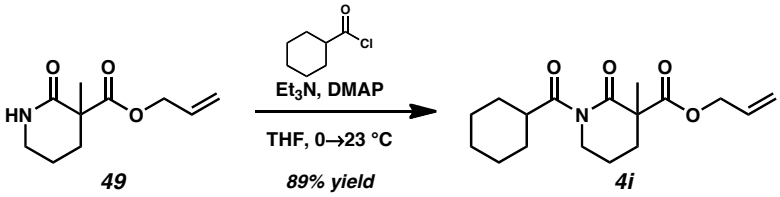


2,3-Dihydropyridin-4-one 30d. $Pd_2(dba)_3$ (1.4 mg, 0.0015 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 2.2 mg, 0.00375 mmol, 12.5 mol %) were added to an oven-dried Schlenk tube equipped with a magnetic stir bar, and the tube was backfilled with argon 3 times. The tube was charged with toluene (1 mL) and heated at 40 °C for 30 min, generating a red/orange solution. 2,3-Dihydropyridin-4-one **29d** (11.9 mg, 0.03 mmol, 1.00 equiv) were added and the tube was lowered into a heating block (40 °C). After 3 h, TLC analysis indicated the reaction was complete. Consequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, 10 x 2 cm, 50% EtOAc in hexanes) to afford dihydropyridine-4-one **30d** (8.6 mg, 0.0242 mmol, 81% yield) as yellow oil; R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.66 (s, 1H), 5.82 (ddt, J = 17.4, 10.2, 7.4 Hz, 1H), 5.62 (s, 1H), 5.10–5.03 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.39 (s, 2H), 3.37 (td, J = 6.5, 1.5 Hz, 2H), 2.99–2.89 (m, 2H), 2.43 (ddt, J = 13.9, 7.2, 1.3 Hz, 1H), 2.25 (ddt, J = 14.0, 7.7, 1.1 Hz, 1H), 1.74 (hd, J = 6.6, 5.0 Hz, 1H), 1.66 (dd, J = 14.1, 6.5 Hz, 1H), 1.44 (dd, J = 14.1, 5.1 Hz, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 155.6, 151.4, 148.0, 134.7, 128.7, 120.8, 117.9, 110.4, 108.3, 94.3, 58.9, 56.0, 48.9, 46.1, 41.7, 39.2, 28.4, 25.1, 24.5, 24.1; IR (Neat Film NaCl) 2953, 1622, 1586,

1549, 1495, 1464, 1342, 1212, 1173, 1110, 1016, 913, 794 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{30}NO_3$ $[M+H]^+$: 356.2147, found 356.2221; $[\alpha]_D^{25.0}$ +32.49 (c 0.71, $CHCl_3$, 90% ee); HPLC conditions: 30% IPA in hexanes, 1 mL/min, Chiralpak AD column, λ = 254 nm, t_R (min): major = 21.87, minor = 18.59.

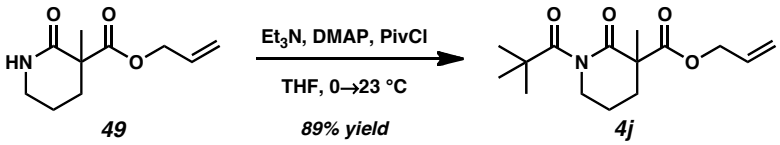
1.4.2.4 Preparation of Lactams

1.4.2.4.6 *Lactam Allylic Alkylation Precursors*



Lactam 4i. Lactam **49**[10] (117.8 mg, 0.597 mmol, 1.00 equiv) was transferred to a flame-dried 15 mL round-bottom flask using THF (4 x 0.5 mL + 1 x 0.4 mL rinses, total = 2.4 mL, 0.25 M). Et_3N (250 µL, 1.79 mmol, 3.00 equiv) and DMAP (9.3 mg, 0.0761 mmol, 13 mol%) were added and the flask was lowered into a 0 °C bath (ice/water). Cyclohexanecarbonyl chloride (160 µL, 1.20 mmol, 2.00 equiv) was added dropwise, and the reaction mixture transitioned from a solution to a white slurry. The ice bath expired gradually as the reaction was stirred overnight. After 15 h of stirring, no starting material remained by TLC analysis. The reaction was subsequently quenched with brine (15 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with EtOAc. The combined organics (100 mL) were rinsed twice with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100%

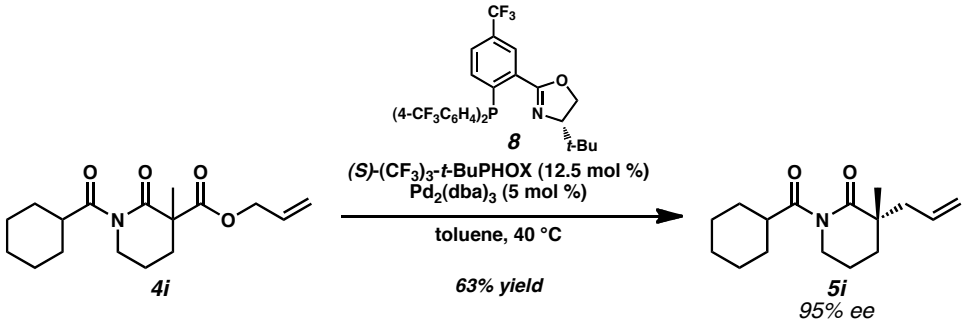
hexanes→10% EtOAc in hexanes) to afford lactam **4i** (163.5 mg, 0.532 mmol, 89% yield) as a yellow oil; R_f = 0.60 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dddd, J = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.32 (dq, J = 17.2, 1.5 Hz, 1H), 5.25 (dq, J = 10.4, 1.2 Hz, 1H), 4.64 (ddt, J = 5.8, 2.5, 1.3 Hz, 2H), 3.77 (ddd, J = 13.1, 7.7, 5.1 Hz, 1H), 3.58 (dddd, J = 13.4, 7.0, 5.0, 1.1 Hz, 1H), 3.27 (tt, J = 11.4, 3.2 Hz, 1H), 2.42 (dddd, J = 13.4, 6.0, 4.9, 0.9 Hz, 1H), 1.95 (dtd, J = 10.5, 3.5, 1.8 Hz, 1H), 1.92–1.80 (m, 3H), 1.79–1.70 (m, 3H), 1.67 (dtt, J = 10.8, 3.2, 1.5 Hz, 1H), 1.52 (s, 3H), 1.47–1.34 (m, 2H), 1.34–1.16 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.3, 173.5, 172.7, 131.4, 119.2, 66.4, 53.5, 45.7, 44.6, 33.1, 30.1, 29.6, 26.1, 25.9, 25.8, 23.0, 20.3; IR (Neat Film NaCl) 3086, 2931, 2855, 1738, 1694, 1652, 1479, 1451, 1378, 1330, 1301, 1249, 1218, 1196, 1159, 1134, 1073, 1053, 1032, 981, 957, 939, 896, 887, 842, 796, 773 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{26}O_4N$ $[M+H]^+$: 308.1856, found 308.1871.



Lactam 4j. Lactam **49**[9] (480 mg, 2.4 mmol, 1.0 equiv) in a 25 mL round-bottom flask equipped with a magnetic stir bar was taken up in THF (9.6 mL, 0.25 M). Et_3N (1.0 mL, 7.2 mmol, 3.0 equiv) and DMAP (29 mg, 0.24 mmol, 0.10 equiv) were added and the flask was lowered into a 0 °C bath (ice/water). Pivaloyl chloride (0.59 mL, 4.8 mmol, 2.0 equiv) was added dropwise and the reaction mixture transitioned from a solution to a white slurry. The ice bath expired gradually as the reaction was stirred overnight. After 24 h of stirring, TLC analysis indicated that conversion had ceased at approximately

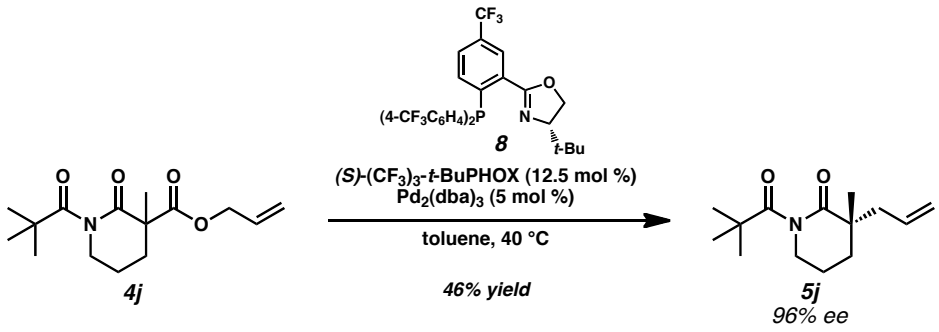
90%. The reaction was subsequently diluted with 20 mL EtOAc, quenched with brine (20 mL), and transferred to a separatory funnel where the aqueous layer was extracted three times with EtOAc (20 mL). The combined organics were washed twice with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 11 x 3 cm, 20% EtOAc in hexanes) to afford lactam **4j** (612 mg, 2.18 mmol, 89% yield) as a pale yellow oil; R_f = 0.37 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.70–4.59 (m, 2H), 3.62 (ddd, *J* = 12.8, 8.2, 4.9 Hz, 1H), 3.45 (dddd, *J* = 12.4, 6.2, 4.9, 1.0 Hz, 1H), 2.40 (dddd, *J* = 13.6, 7.1, 4.0, 1.0 Hz, 1H), 2.01–1.83 (m, 2H), 1.74 (ddd, *J* = 13.7, 9.5, 4.1 Hz, 1H), 1.52 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 172.5, 131.7, 119.2, 66.4, 52.5, 47.9, 44.5, 33.6, 28.0, 22.8, 20.3; IR (Neat Film NaCl) 3434, 2090, 1650, 1257, 1125 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{24}NO_4$ $[M+H]^+$: 282.1700, found 282.1705.

1.4.2.4.7 *Lactam Allylic Alkylation Products*



Lactam 5i. $Pd_2(dba)_3$ (16.4 mg, 0.0150 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 22.1 mg, 0.0374 mmol, 12.5 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was

charged with toluene (2.06 mL) and stirred at ambient temperature for 30 min, generating a red/orange solution. Lactam **4i** (91.9 mg, 0.299 mmol, 1.00 equiv) was transferred to the scintillation vial with toluene (3 x 2 mL + 1 x 1 mL rinses, total = 9.06 mL, 0.033 M) producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 7 days, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford recovered lactam **4i** (17.2 mg, 0.0560 mmol, 19% recovered) and lactam **5i** (49.8 mg, 0.189 mmol, 63% yield, 78% yield based on recovered lactam **4i**) as a yellow oil; R_f = 0.73 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, J = 16.6, 10.4, 7.8, 6.9 Hz, 1H), 5.13–5.06 (m, 2H), 3.76–3.67 (m, 1H), 3.57–3.49 (m, 1H), 3.18 (tt, J = 11.4, 3.3 Hz, 1H), 2.51 (ddt, J = 13.6, 6.9, 1.2 Hz, 1H), 2.27 (ddt, J = 13.6, 7.8, 1.1 Hz, 1H), 1.90 (dddd, J = 12.7, 5.5, 2.9, 1.4 Hz, 1H), 1.87–1.72 (m, 7H), 1.67 (dtt, J = 10.8, 3.5, 1.5 Hz, 1H), 1.62–1.56 (m, 1H), 1.42 (dtdd, J = 12.9, 12.0, 11.2, 3.2 Hz, 2H), 1.35–1.19 (m, 2H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 179.5, 133.5, 118.9, 46.1, 45.8, 45.0, 44.5, 33.3, 30.0, 30.0, 26.1, 25.9, 25.9, 25.8, 19.8; IR (Neat Film NaCl) 3076, 2930, 2854, 1690, 1478, 1451, 1375, 1329, 1313, 1286, 1246, 1198, 1158, 1136, 1089, 1072, 1031, 996, 975, 919, 759 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{26}O_2N$ $[M+H]^+$: 264.1958, found 264.1945; $[\alpha]_D^{25.0}$ –96.13 (c 1.06, $CHCl_3$, 95% ee); JASCO SFC conditions: 1% IPA in CO_2, 5 mL/min, Chiralcel OJ-H column, λ = 222 nm, t_R (min): major = 2.53, minor = 2.13.

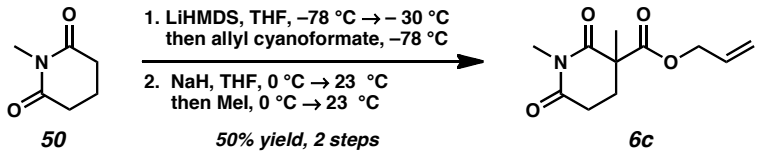


Lactam 5j. $Pd_2(pmdba)_3$ (27 mg, 25 μmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 37 mg, 63 μmol, 12.5 mol %) were added to an oven-dried 20 mL scintillation vial equipped with a magnetic stir bar in a glove box. The vial was charged with toluene (12 mL) and stirred at ambient temperature (28 °C) for 30 min, resulting in a deep orange solution. Lactam **4j** (140 mg, 0.50 mmol, 1.0 equiv) was transferred to the scintillation vial with toluene (2 mL, total = 15 mL, 0.033 M), producing a light green solution. The vial was sealed with a Teflon-lined cap and lowered into a heating block (40 °C). After 16 days, TLC analysis indicated that conversion had ceased at approximately 50% and the vial was removed from the glove box and the reaction was filtered through a silica gel plug, rinsed with Et_2O, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 15 x 2.5 cm, 5% EtOAc in hexanes) to afford lactam **5j** (54 mg, 0.23 mmol, 46% yield) as a colorless oil; R_f = 0.58 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (dddd, *J* = 17.1, 10.2, 7.8, 7.0 Hz, 1H), 5.16–5.05 (m, 2H), 3.53–3.38 (m, 2H), 2.51 (ddt, *J* = 13.7, 7.0, 1.3 Hz, 1H), 2.28 (ddt, *J* = 13.7, 7.7, 1.1 Hz, 1H), 1.92–1.80 (m, 3H), 1.61–1.58 (m, 1H), 1.27 (s, 9H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 179.0, 133.7, 118.9, 48.5, 44.2, 43.4, 43.3, 33.4, 28.1, 25.0, 19.8; IR (Neat Film NaCl) 2963, 1684, 1482, 1457, 1391, 1282, 1259, 1156, 917 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{24}NO_2$ $[M+H]^+$: 238.1802,

found 238.1809; $[\alpha]_D^{25.0}$ –7.13 (c 2.45, $CHCl_3$, 96% ee); HPLC conditions: 5% IPA in hexanes, 1 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 7.95, minor = 6.52.

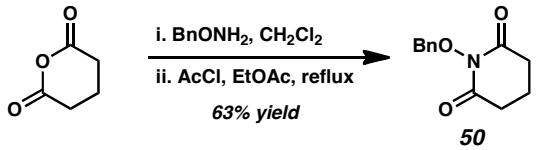
1.4.2.5 Preparation of Imides

1.4.2.5.8 *Imide Allylic Alkylation Precursors*



***N*-Methyl imide 6c.** A flame-dried 200 mL round-bottom flask containing a magnetic stir bar was cycled into a glove box and loaded with LiHMDS (5.69 g, 34.0 mmol, 1.7 equiv). The flask was removed from the glove box, reconnected to a manifold, and charged with THF (100 mL, 0.2 M) and lowered into a –78 °C bath. Imide **50**[48] (2.54 g, 20.0 mmol, 1.0 equiv) was added neat. After 1 h at –78 °C, the solution was warmed to 30 °C and stirred for 30 min before cooling back to –78 °C. Allyl cyanoformate (2.67 g, 24.0 mmol, 1.2 equiv) was added neat and the reaction was stirred for 1.5 h before TLC analysis indicated consumption of starting material. The reaction was subsequently quenched with brine and transferred to a separatory funnel where the aqueous layer was extracted with EtOAc (4 x 50 mL). The combined organics were rinsed twice with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 5 cm x 7 inches, 25%→30%→40% EtOAc in hexanes) to afford an intermediate oil (2.63 g, 0.45 mmol, 62% yield) that was moved on to the next step.

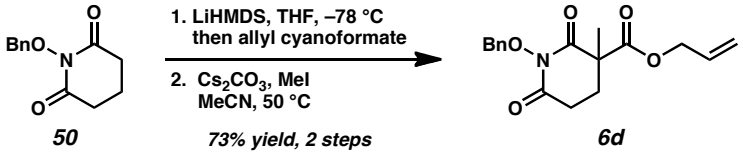
A flame-dried 200 mL flask equipped with a magnetic stir bar was charged with sodium hydride (60% in mineral oil, 312.5 mg, 7.81 mmol, 1.1 equiv) and THF (71 mL, 0.1 M) and cooled to 0 °C. A portion of the oil from the previous step (1.5 g, 7.10 mmol, 1.0 equiv) was added neat. After 1.5 h at 0 °C, the reaction was warmed to room temperature and stirred for 1 h before cooling back to 0 °C. Methyl iodide (886 μL, 14.20 mmol, 2.0 equiv) was added and the reaction was stirred for 2 h before warming to room temperature. After 15 h, the reaction was poured over a mixture of water and brine and transferred to a separatory funnel where the aqueous layer was extracted with EtOAc (4 x 50 mL). The combined organics were rinsed twice with aq. $Na_2S_2O_3$ (sat. solution half diluted) and twice with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 5 cm x 8 inches, 10% →20% EtOAc in hexanes) to afford imide **6c** (1.28 g, 5.69 mmol, 80% yield, 50% yield over two steps); R_f = 0.32 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 5.29 (dq, J = 17.2, 1.5 Hz, 1H), 5.25 (dq, J = 10.5, 1.2 Hz, 1H), 4.63 (ddt, J = 5.6, 4.1, 1.4 Hz, 2H), 3.18 (s, 3H), 2.72 (ddd, J = 18.1, 5.4, 4.4 Hz, 1H), 2.64 (ddd, J = 17.9, 11.6, 5.4 Hz, 1H), 2.35 (ddd, J = 13.9, 5.4, 4.4 Hz, 1H), 1.89 (ddd, J = 13.9, 11.6, 5.4 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 171.8, 171.3, 131.2, 119.3, 66.5, 50.9, 30.0, 28.7, 27.3, 21.9; IR (Neat Film NaCl) 2987, 2943, 1726, 1678, 1458, 1416, 1381, 1356, 1305, 1261, 1247, 1182, 1106, 1036, 993, 938 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{18}NO_4$ $[M+H]^+$: 226.1074, found 226.1078.



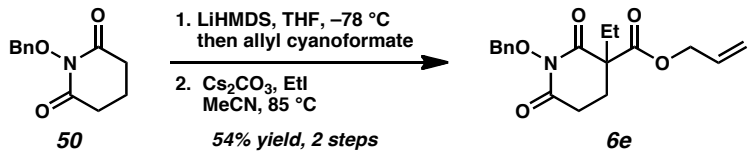
50

***N*-benzyloxyimide 50.** Benzyloxyamine hydrochloride (3.15 g, 19.7 mmol) in a 100 mL round-bottom flask was taken up in dichloromethane (30 mL) and saturated aqueous K_2CO_3 (30 mL) and stirred for 30 min. The mixture was transferred to a separatory funnel and the phases were separated. The aqueous phase was extracted twice with dichloromethane (30 mL), the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. A portion of the resulting crude colorless oil (1.23 g, 10.0 mmol, 1.00 equiv) was diluted with dichloromethane (10 mL, 1.0 M) in a 50 mL round-bottom flask and glutaric anhydride (1.14 g, 10.0 mmol, 1.00 equiv) was added. An exotherm was observed, and the mixture was immediately concentrated under reduced pressure. The resulting residue was taken up in EtOAc (13 mL, 0.75 M) and acetyl chloride (2.00 mL, 2.81 mmol, 2.81 equiv) was added. A water condenser was affixed and the reaction was heated to a gentle reflux (oil bath, 85 °C) for 18 h. The reaction was diluted with EtOAc (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude solid was purified by flash column chromatography (SiO_2, 6 x 5 cm, 20% EtOAc in hexanes→50% Et_2O in dichloromethane) to afford *N*-benzyloxyimide **50** (1.37 g, 6.25 mmol, 63% yield) as a white solid; R_f = 0.64 (20% Et_2O in methylene chloride); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.45 (m, 2H), 7.41–7.29 (m, 3H), 5.01 (s, 2H), 2.74–2.60 (m, 4H), 1.94–1.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.48 , 133.95 , 130.09 , 129.23 , 128.51 , 78.17 , 33.47 , 17.05; IR (Neat Film NaCl) 3033, 2957, 2902, 1689, 1457, 1381, 1350, 1331, 1251, 1175, 1134, 1087, 1056, 999,

968, 919, 893, 838, 759 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{14}NO_3$ $[M+H]^+$: 220.0968, found 220.0971.

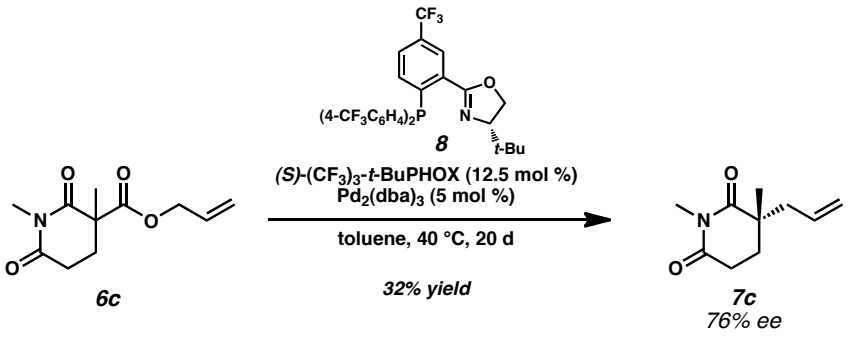


***N*-Benzyloxy imide 6d.** Acylation performed in manner analogous to *N*-methyl imide **6c** at –78 °C using *N*-benzyloxy imide **50** as starting material. Alkylation performed in manner analogous to β-ketoester **45a** at 50 °C. *N*-Benzyloxy imide **6d** was isolated after flash column chromatography (SiO_2, 17 to 25% EtOAc in hexanes) as a colorless oil (73% yield over two steps); R_f = 0.20 (20% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.37 (m, 3H), 5.87 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.01 (s, 2H), 4.66 (ddt, *J* = 13.0, 5.9, 1.3 Hz, 1H), 4.65 (ddt, *J* = 13.0, 5.9, 1.3 Hz, 1H), 2.72 (m, 2H), 2.30 (ddd, *J* = 14.1, 5.2, 4.0 Hz, 1H), 1.86 (ddd, *J* = 14.1, 11.8, 5.5 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ170.7, 167.9, 167.4, 133.9, 130.9, 130.1, 129.2, 128.5, 119.9, 77.9, 66.9, 52.1, 30.5, 28.5, 21.6; IR (Neat Film NaCl) 2943, 1738, 1733, 1708, 1451, 1255, 1200, 1168, 976 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{20}NO_5$ $[M+H]^+$: 318.1336, found 318.1339.

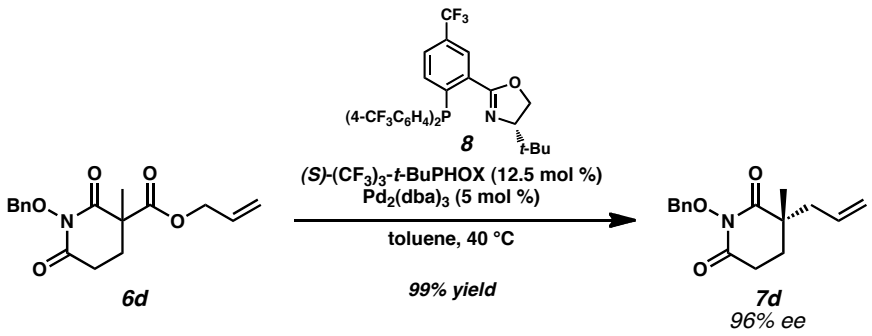


***N*-Benzyloxy imide 6e.** Acylation performed in manner analogous to *N*-methyl imide **6c** at –78 °C using *N*-benzyloxy imide **50** as starting material. Alkylation performed in manner analogous to β-ketoester **45a** at 85 °C using ethyl iodide. *N*-Benzyloxy imide **6e** was isolated after flash column chromatography (SiO_2, 14 to 20% EtOAc in hexanes) as a colorless oil (54% yield over two steps); R_f = 0.24 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.37 (m, 3H), 5.87 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.34 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.0 (s, 2H), 4.66 (dt, *J* = 5.9, 1.3 Hz, 2H), 2.74 (m, 2H), 2.22 (ddd, *J* = 14.0, 5.2, 3.5 Hz, 1H), 2.05(m, 2H), 1.96 (ddd, *J* = 14.0, 12.3, 5.4 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ170.2, 167.5, 167.1, 134.0, 131.0, 130.1, 129.3, 128.6, 120.0, 77.9, 66.8, 56.2, 30.4, 28.3, 24.8, 9.0; IR (Neat Film NaCl) 2943, 1733, 1713, 1648, 1454, 1237, 1190, 1168, 976, 752 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{22}NO_5$ $[M+H]^+$: 332.1492, found 332.1493.

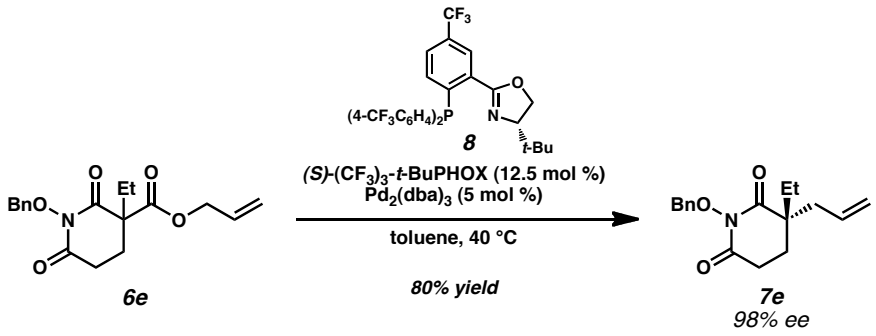
1.4.2.5.9 *Imide Allylic Alkylation Products*



***N*-Methyl imide 7c.** Prepared in a manner analogous to lactam **5h** using *N*-methyl imide **6c** as starting material. After 20 d, the reaction was filtered, concentrated, and *N*-Methyl imide **7c** was isolated following flash column chromatography (SiO_2, 3 cm x 10 inches, 5%→7%→9%→10% →12% EtOAc in hexanes) as an oil (32% yield); R_f = 0.36 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (dddd, J = 17.1, 10.2, 7.6, 7.1 Hz, 1H), 5.15–5.08 (m, 2H), 3.12 (s, 3H), 2.75–2.62 (m, 2H), 2.47 (ddt, J = 13.8, 7.1, 1.2 Hz, 1H), 2.29 (ddt, J = 13.8, 7.7, 1.1 Hz, 1H), 1.92 (ddd, J = 14.3, 8.6, 5.9 Hz, 1H), 1.66 (ddd, J = 14.0, 7.1, 5.8 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 172.5, 132.8, 119.5, 42.6, 41.7, 29.3, 27.8, 27.0, 23.4; IR (Neat Film NaCl) 2971, 2937, 2876, 1723, 1674, 1464, 1415, 1378, 1356, 1291, 1240, 1110, 1036, 998, 919 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{16}NO_2$ $[M+H]^+$: 182.1176, found 182.1178; $[\alpha]_D^{25.0}$ –54.19 (c 1.64, $CHCl_3$, 76% ee); HPLC conditions: 3% IPA in hexanes, 1 mL/min, Chiralpak AD column, λ = 210 nm, t_R (min): major = 11.94, minor = 17.86.



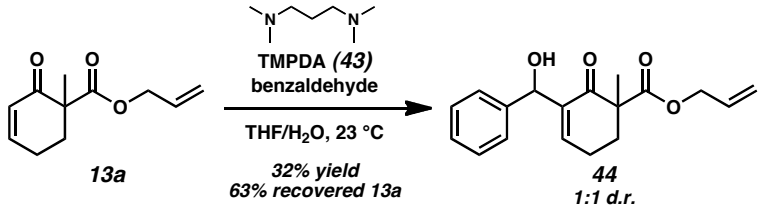
***N*-Benzyloxy imide 7d.** Prepared in a manner analogous to lactam **5h** using *N*-benzyloxy imide **6d** as starting material. *N*-Benzyloxy imide **7d** was isolated after flash column chromatography (SiO_2, 20% EtOAc in hexanes) as a colorless oil (99% yield); R_f = 0.29 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.36 (m, 3H), 5.64 (dddd, *J* = 17.2, 10.2, 7.7, 7.1 Hz, 1H), 5.09–5.15 (m, 2H), 5.0 (s, 2H), 2.66–2.77 (m, 2H), 2.43 (ddt, *J* = 13.9, 7.1, 1.2 Hz, 1H), 2.26 (ddt, *J* = 13.9, 7.7, 1.2 Hz, 1H), 1.87 (ddd, *J* = 14.3, 8.5, 5.9 Hz, 1H), 1.60 (ddd, *J* = 14.3, 7.0, 5.7 Hz, 1H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 168.1, 133.9, 132.3, 130.3, 129.2, 128.5, 119.9, 78.0, 43.1, 42.3, 29.7, 27.6, 23.1; IR (Neat Film NaCl) 3067, 2974, 2935, 1740, 1703, 1700, 1456, 1172, 978, 748 cm^{-1}; HRMS (MM: ESI-APCI) *m*/*z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1437; $[\alpha]_D^{25.0}$ –58.59 (c 1.26, $CHCl_3$, 96% ee); Thar SFC conditions: 5% MeOH in CO_2, 3 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 4.03, minor = 3.64.



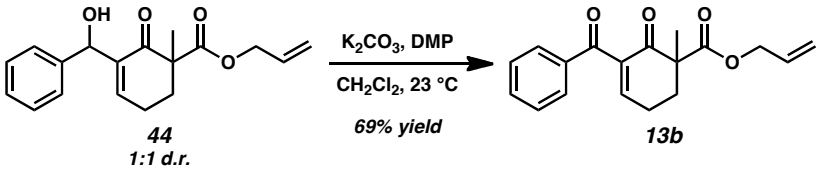
***N*-Benzyloxy imide 7e.** Prepared in a manner analogous to lactam **5h** using *N*-benzyloxy imide **6e** as starting material. *N*-Benzyloxy imide **7e** was isolated after flash column chromatography (SiO_2, 20% EtOAc in hexanes) as a colorless oil (80% yield); R_f = 0.20 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.36 (m, 3H), 5.63 (dddd, *J* = 17.3, 10.3, 7.7, 6.9 Hz, 1H), 5.08–5.10 (m, 2H), 4.99 (s, 2H), 2.67–2.76 (m, 2H), 2.46 (ddt, *J* = 14.0, 6.9, 1.3 Hz, 1H), 2.27 (ddt, *J* = 14.0, 7.7, 1.1 Hz, 1H), 1.80 (ddd, *J* = 14.2, 7.9, 6.4 Hz, 1H), 1.76–1.71 (m, 1H), 1.70 (dq, *J* = 14.2, 7.5 Hz, 1H), 1.62 (dq, *J* = 14.2, 7.5 Hz, 1H), 0.86 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 168.0, 134.0, 132.6, 130.2, 129.2, 128.5, 119.6, 78.0, 46.5, 40.0, 29.5, 28.6, 24.7, 8.2; IR (Neat Film NaCl) 3033, 2972, 1739, 1702, 1699, 1455, 1169, 977, 751 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found 288.1591; $[\alpha]_D^{25.0}$ –35.98 (c 1.98, $CHCl_3$, 98% ee); Thar SFC conditions: 1% MeOH in CO_2, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, t_R (min): major = 14.34, minor = 13.39.

1.4.2.6 Preparation of Enones and Diosphenol Ethers

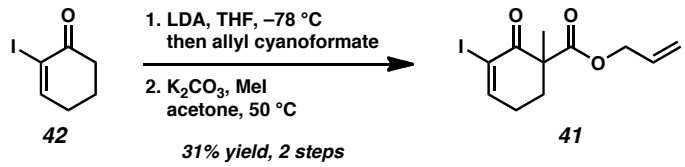
1.4.2.6.10 Enone and Diosphenol Ether Allylic Alkylation Precursors



Alcohol 44. Procedure adapted from the literature precedent of Kim.[44] A 15 mL round-bottom flask equipped with a stir bar was charged with enone **13a** (852.1 mg, 4.39 mmol, 1.94 equiv), THF (1.4 mL, 1.6 M), benzaldehyde (230 μL, 2.26 mmol, 1.00 equiv), H_2O (1.4 mL, 1.6 M), and TMPDA (**43**, 380 μL, 2.27 mmol, 1.00 equiv). The reaction mixture was a yellow suspension that transitioned to orange over time. After 6 days, the reaction was diluted with H_2O (10 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 25.5 x 3 cm, 100% hexanes→5%→10%→15%→20% EtOAc in hexanes) to afford recovered enone **13a** (536.0 mg, 2.76 mmol, 63% recovered) pale yellow oil and alcohol **44** (217.7 mg, 0.725 mmol, 32% yield, 45% yield based on recovered enone **13a**) as a yellow oil; R_f = 0.28 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) ~1:1 mixture of diastereomers, see Figure 1.42.1; IR (Neat Film NaCl) 3503 (broad), 3061, 3030, 2980 2934, 1735, 1672, 1492, 1452, 1424, 1379, 1291, 1246, 1187, 1165, 1111, 1018, 982, 936, 760 cm^{-1}; HRMS (EI+) calc'd for $C_{18}H_{20}O_4$ $[M+\bullet]^+$: 300.1362, found 300.1376.



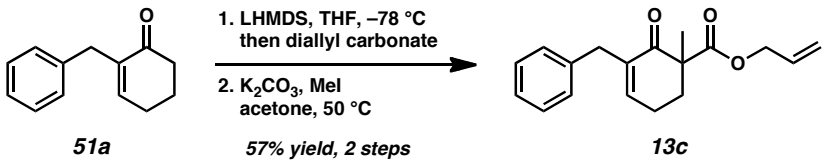
Enone 13b. A scintillation vial containing alcohol **44** (44.5 mg, 0.148 mmol, 1.00 equiv) was equipped with a stir bar, connected to a manifold, backfilled with Ar, and charged with CH_2Cl_2 (1 mL, 0.15 M). K_2CO_3 (62.5 mg, 0.452 mmol, 3.05 equiv) and DMP (96.3 mg, 0.227 mmol, 1.53 equiv) were added simultaneously to the vial. After 2 h of stirring, no starting material was detected by TLC analysis. Consequently, the reaction was diluted with CH_2Cl_2 (1 mL), filtered through a short celite plug rinsing with CH_2Cl_2, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 27 x 1 cm, 0.1% Et_3N in hexanes→0.1% Et_3N and 10% EtOAc in hexanes) to afford enone **13b** (30.4 mg, 0.102 mmol, 69% yield) as a yellow oil; Rf = 0.43 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 8.11–8.07 (m, 2H), 7.15–7.08 (m, 3H), 6.62 (ddd, J = 5.0, 2.9, 1.2 Hz, 1H), 5.61 (ddt, J = 17.1, 10.3, 5.7 Hz, 1H), 5.05 (dq, J = 17.2, 1.5 Hz, 1H), 4.92 (dq, J = 10.4, 1.3 Hz, 1H), 4.37 (dt, J = 5.7, 1.4 Hz, 2H), 2.11 (dddd, J = 13.5, 4.8, 3.4, 1.2 Hz, 1H), 2.04 (dddd, J = 20.1, 9.6, 5.1, 2.9 Hz, 1H), 1.59 (dtdd, J = 20.1, 5.1, 3.4, 1.4 Hz, 1H), 1.36–1.27 (m, 1H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 194.0, 193.6, 172.1, 150.9, 141.4, 137.6, 133.1, 132.0, 129.9, 128.5, 118.5, 65.9, 53.8, 33.5, 23.6, 20.6; IR (Neat Film NaCl) 3063, 3027, 2981, 2935, 2873, 2855, 2280, 1732, 1668, 1621, 1598, 1581, 1449, 1423, 1378, 1358, 1293, 1265, 1244, 1178, 1157, 1111, 988, 940, 814, 769, 712; HRMS (FAB+) cal'd for $C_{18}H_{18}O_4$ $[M+\bullet]^+$: 298.1205, found 298.1219.



α-Iodoenone 41. A 50 mL round-bottom flask equipped with a stir bar was charged with diisopropyl amine (450 μL, 3.21 mmol, 1.10 equiv) and THF (7 mL). The flask was lowered into a 0 °C bath (water/ice) and *n*-BuLi (1.26 mL, 2.43 M in hexanes, 3.06 mmol, 1.05 equiv) was added dropwise over several minutes. The reaction was stirred for 15 min before the ice bath was removed and replaced with a –78 °C bath (acetone/dry ice). α-Iodoenone **42** (641.3 mg, 2.91 mmol, 1.00 equiv) was transferred via cannula to the flask using several THF rinses (1 x 6 mL and 2 x 1 mL rinses, total added = 15 mL, 0.19 M), producing a yellow solution. The reaction was stirred for 1 h before allyl cyanoformate (330 μL, 3.06 mmol, 1.05 equiv) was added dropwise. After 2.5 h, no starting material was observed by ^{1}H NMR analysis and the reaction was subsequently quenched after an additional hour with sat. NH_4Cl solution (10 mL) and allowed to warm to room temperature. The reaction contents were transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (100 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 27.5 x 3 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford a yellow oil (R_f = 0.52, 30% EtOAc in hexanes) that was moved on to the next step.

The resulting yellow oil was transferred to an argon filled 25 mL Schlenk bomb (14/20 joint off of an 8 mm Kontes valve) equipped with a magnetic stir bar using several acetone rinses (ACS reagent grade, 5 x 2 mL). Additional acetone (3.2 mL, total added =

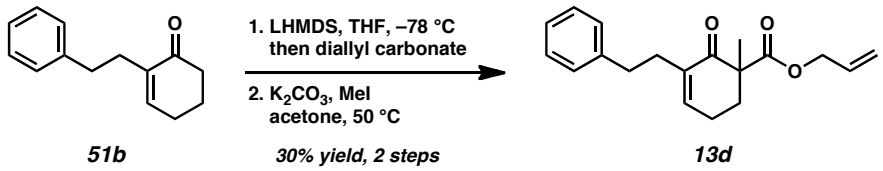
13.2 mL, 0.10 M), K_2CO_3 (367.6 mg, 2.66 mmol, 2.01 equiv), and MeI (170 μL, 2.73 mmol, 2.06 equiv) were added to the bomb. The Kontes valve was sealed, the bomb was lowered into a preheated oil bath (50 °C), and the reaction was stirred vigorously. After 18 h, ^{1}H NMR analysis indicated residual starting material, and consequently more MeI (90 μL, total added = 260 μL, 4.18 mmol, 3.15 equiv) was added. After an additional 21 h, no starting material remained by ^{1}H NMR analysis. Subsequently, the bomb was removed from the oil bath and allowed to cool to room temperature. The reaction contents were filtered through a celite plug rinsing with EtOAc and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 28 x 2 cm, 100% hexanes→5% EtOAc in hexanes) to afford α-iodoenone **41** (277.8 mg, 0.868 mmol, 31% yield over two steps) as a pale yellow oil; R_f = 0.63 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (ddd, J = 4.7, 3.3, 1.0 Hz, 1H), 5.85 (dddd, J = 17.2, 10.8, 5.5, 5.5 Hz, 1H), 5.28 (dq, J = 17.2, 1.5 Hz, 1H), 5.22 (dm, J = 10.5 Hz, 1H), 4.64 (dddd, J = 11.5, 6.3, 4.8, 1.5 Hz, 1H), 4.57 (dddd, J = 11.4, 6.2, 4.7, 1.5 Hz, 1H), 2.60–2.51 (m, 2H), 2.42–2.33 (m, 1H), 2.02–1.95 (m, 1H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 171.6, 158.1, 131.4, 118.7, 102.0, 66.1, 53.5, 33.3, 27.9, 21.3; IR (Neat Film NaCl) 3085, 2982, 2936, 2874, 2826, 1735, 1696, 1648, 1595, 1457, 1422, 1378, 1323, 1293, 1244, 1178, 1142, 1110, 1089, 1051, 966, 956, 930, 890, 864, 833, 782, 730 cm^{-1}; HRMS (FAB+) calc'd for $C_{11}H_{14}O_3I$ $[M+H]^+$: 320.9988, found 320.9993.



Enone 13c. A 25 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box, loaded with LHMDS (527.6 mg, 3.15 mmol, 2.10 equiv), removed from the glove box, and connected to an Ar-filled manifold. The flask was charged with THF (1 mL) and lowered into a 0 °C bath (ice/water). Enone **51a**[49] (279.0 mg, 1.50 mmol, 1.00 equiv) was cannula transferred slowly from a scintillation vial to the flask using several THF rinses (1 x 4 mL + 2 x 0.5 mL, total added = 6 mL, 0.25 M), generating a bright red/pink solution. After the addition was complete, the 0 °C bath was removed and the reaction was allowed to warm to room temperature. After 30 min, the flask was lowered back into the 0 °C bath and diallyl carbonate (230 μL, 1.60 mmol, 1.07 equiv) was added dropwise, generating an orange solution. The bath was allowed to expire overnight. After 18 h, the reaction was quenched with sat. NH_4Cl sol. (10 mL) and transferred to a separatory funnel where the aqueous layer was extracted five times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 21 x 2 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford a yellow oil.

The resulting yellow oil (285.8 mg, 1.06 mmol, 1.00 equiv) was transferred to an Ar-filled 25 mL Schlenk bomb (14/20 joint off of an 8 mm Kontes valve) equipped with a magnetic stir bar using several acetone rinses (1 x 1.5 mL + 3 x 0.5 mL, total added = 3 mL, 0.35 M). K_2CO_3 (292.7 mg, 2.12 mmol, 2.00 equiv) and methyl iodide (180 μL,

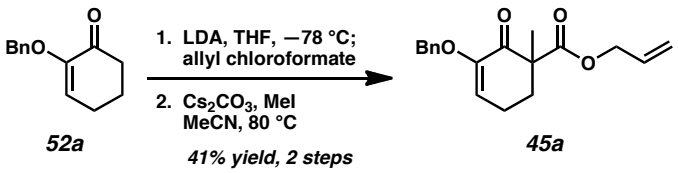
2.89 mmol, 2.73 equiv) were added to the bomb. The Kontes valve was sealed, the bomb was lowered into a preheated oil bath (50 °C), and the reaction was stirred vigorously. After 11 h, ^{1}H NMR analysis indicated residual starting material, and consequently more methyl iodide (130 μL, total added = 310 μL, 4.98 mmol, 4.71 equiv) was added. After an additional 8.5 h, no starting material remained by ^{1}H NMR analysis. Subsequently, the bomb was removed from the oil bath and allowed to cool to room temperature. The reaction contents were filtered through a celite plug rinsing with CH_2Cl_2 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 26.5 x 1.5 cm, 100% hexanes→5% EtOAc in hexanes) to afford enone **13c** (271.2 mg, 0.954 mmol, 64% yield over two steps, 90% purity) as a yellow oil. This yellow oil was diluted in EtOAc (50 mg/mL) and purified further by preparative HPLC (10% EtOAc in hexanes) to afford analytically pure enone **13c** (242.8 mg, 0.851 mmol, 57% yield over two steps) as a pale yellow oil; R_f = 0.59 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H), 7.21–7.14 (m, 3H), 6.50–6.45 (m, 1H), 5.78 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.24 (dq, J = 17.2, 1.5 Hz, 1H), 5.19 (dq, J = 10.5, 1.1 Hz, 1H), 4.53 (dm, J = 5.6 Hz, 2H), 3.58 (dq, J = 15.7, 1.7 Hz, 1H), 3.51 (dq, J = 15.6, 1.7 Hz, 1H), 2.52–2.40 (m, 2H), 2.34–2.24 (m, 1H), 1.94–1.86 (m, 1H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 172.6, 145.1, 139.5, 138.8, 131.8, 129.3, 128.5, 126.2, 118.4, 65.8, 53.6, 36.0, 33.7, 23.6, 20.6; IR (Neat Film NaCl) 3084, 3061, 3027, 2980, 2934, 1734, 1685, 1603, 1496, 1453, 1430, 1375, 1292, 1246, 1166, 1111, 1077, 1029, 984, 747 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1485, found 285.1482.



Enone 13d. A 25 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box, loaded with LHMDS (215.6 mg, 1.29 mmol, 2.12 equiv), removed from the glove box, and connected to an Ar-filled manifold. The flask was charged with THF (0.5 mL) and lowered into a 0 °C bath (ice/water). Enone **51b**[49] (122.0 mg, 0.609 mmol, 1.00 equiv) was cannula transferred slowly from a scintillation vial to the flask using several THF rinses (1 x 1 mL + 2 x 0.5 mL, total added = 2.5 mL, 0.24 M), generating a bright pink solution. After the addition was complete, the 0 °C bath was removed and the reaction was allowed to warm to room temperature. After 30 min, the flask was lowered back into the 0 °C bath and diallyl carbonate (100 μL, 0.697 mmol, 1.14 equiv) was added dropwise. The bath was allowed to expire overnight. After 18 h, the reaction was quenched with sat. NH_4Cl sol. (5 mL) and transferred to a separatory funnel where the aqueous layer was extracted five times with Et_2O. The combined organics (70 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27 x 1.5 cm, 100% hexanes→5% EtOAc in hexanes) to afford a yellow oil.

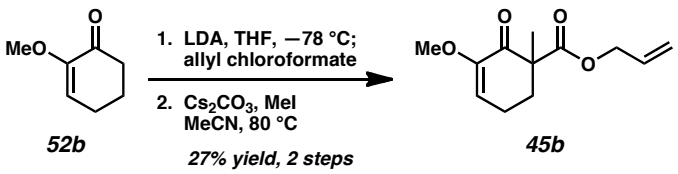
The resulting yellow oil (84.6 mg, 0.298 mmol, 1.00 equiv) was transferred to an Ar-filled 25 mL Schlenk bomb (14/20 joint off of an 8 mm Kontes valve) equipped with a magnetic stir bar using several acetone rinses (4 x 0.5 mL, total added = 2 mL, 0.15 M). K_2CO_3 (87.0 mg, 0.630 mmol, 2.12 equiv) and methyl iodide (100 μL, 1.61 mmol, 5.40 equiv) were added to the bomb. The Kontes valve was sealed, the bomb was lowered

into a preheated oil bath (50 °C), and the reaction was stirred vigorously. After 16 h, ^{1}H NMR analysis indicated residual starting material, and consequently more methyl iodide (130 μL, total added = 310 μL, 4.98 mmol, 4.71 equiv) was added. After an additional 8.5 h, no starting material remained by ^{1}H NMR analysis. Subsequently, the bomb was removed from the oil bath and allowed to cool to room temperature. The reaction contents were filtered through a celite plug rinsing with CH_2Cl_2 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes→2% EtOAc in hexanes) to afford enone **13d** (75.6 mg, 0.253 mmol, 42% yield over two steps, 80% purity) as a yellow oil. This yellow oil was diluted with EtOAc (50 mg/mL) and purified further by preparative HPLC (10% EtOAc in hexanes, 50 mL/min) to afford analytically pure enone **13d** (54.1 mg, 0.181 mmol, 30% yield over two steps) as a pale yellow oil; R_f = 0.67 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.24 (m, 2H), 7.20–7.15 (m, 3H), 6.53 (ddq, J = 4.6, 3.3, 1.0 Hz, 1H), 5.87 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.29 (dq, J = 17.2, 1.5 Hz, 1H), 5.22 (dq, J = 10.5, 1.3 Hz, 1H), 4.65–4.57 (m, 2H), 2.74 (ddd, J = 13.4, 9.7, 6.1 Hz, 1H), 2.67 (ddd, J = 13.4, 9.3, 6.1 Hz, 1H), 2.57 (dddq, J = 13.8, 9.2, 6.4, 1.5 Hz, 1H), 2.52–2.37 (m, 2H), 2.29 (qt, J = 4.9, 1.3 Hz, 1H), 2.25 (ddt, J = 9.9, 4.8, 1.3 Hz, 1H), 1.88 (ddd, J = 13.4, 8.4, 5.3 Hz, 1H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 172.7, 144.5, 142.0, 138.2, 131.8, 128.7, 128.4, 126.0, 118.5, 65.8, 53.6, 34.9, 33.6, 32.5, 23.5, 20.6; IR (Neat Film NaCl) 3026, 2930, 1733, 1683, 1603, 1495, 1456, 1377, 1244, 1167, 1109, 985, 931, 748 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{23}O_3$ $[M+H]^+$: 299.1642, found 299.1638.



β-ketoester 45a. Diisopropylamine (390 μL, 2.78 mmol, 4.46 equiv) in a 10 mL round-bottom flask equipped with a magnetic stir bar was taken up in 2.0 mL THF and lowered into a 0 °C bath (ice/water). To the stirring solution was added *n*-butyl lithium (4.7 M solution in hexanes, 0.583 mL, 2.74 mmol, 4.40 equiv). This solution was stirred for 30 min before transferring the flask to a –78 °C bath (dry ice/acetone) and stirring the mixture for another 15 min. Benzyl diosphenol ether **52a**[50] (126 mg, 0.623 mmol, 1.00 equiv) in 1.1 mL THF (total = 3.1 mL, 0.2 M) was added dropwise by syringe, and the solution was stirred for 2 h. Allyl cyanoformate (270 μL, 2.49 mmol, 4.00 equiv) was added dropwise by syringe, and the reaction was stirred for 8 h until analysis by TLC showed complete consumption of starting material. The reaction was diluted with 2 mL EtOAc and quenched with 1.5 mL each saturated aqueous NH_4Cl and water. The –78 °C bath was removed and the biphasic mixture was warmed to room temperature. The mixture was transferred to a separatory funnel and the phases were separated. The aqueous phase was extracted twice with EtOAc (5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude yellow oil was taken up in acetonitrile (2.0 mL, 0.3 M) in a flame-dried 2-dram vial equipped with a magnetic stir bar. Cs_2CO_3 (264 mg, 0.810 mmol, 1.30 equiv) and methyl iodide (116 μL, 1,86 mmol, 3.00 equiv) were added, and the reaction was blanketed under argon and sealed with a Teflon-lined cap. The vial was placed in a heating block (80 °C) and stirred for 8 h until analysis by TLC showed complete consumption of

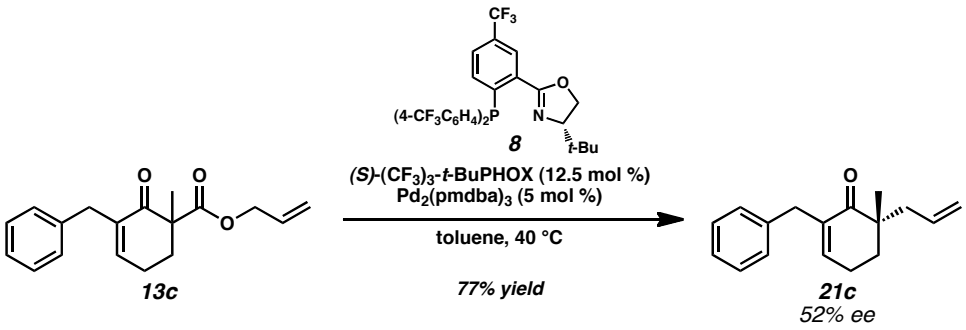
starting material. The reaction was diluted with 5 mL EtOAc, filtered and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 12 x 1.5 cm, 20% Et_2O in hexanes) to afford β-ketoester **45a** (77 mg, 0.26 mmol, 41% yield over two steps) as a colorless oil; R_f = 0.34 (40% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 5.93–5.79 (m, 2H), 5.30 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.23 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.95–4.83 (m, 2H), 4.67–4.52 (m, 2H), 2.50–2.41 (m, 2H), 2.39–2.27 (m, 1H), 1.96–1.83 (m, 1H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 172.3, 149.7, 136.7, 131.7, 128.6, 128.0, 127.3, 118.8, 118.5, 70.1, 65.9, 54.3, 33.7, 21.7, 20.6; IR (Neat Film NaCl) 3394, 2916, 2167, 1996, 1692, 1627, 1455, 1251, 1153, 1110, 1056 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{21}O_4$ $[M+H]^+$: 301.1434, found 301.1422.



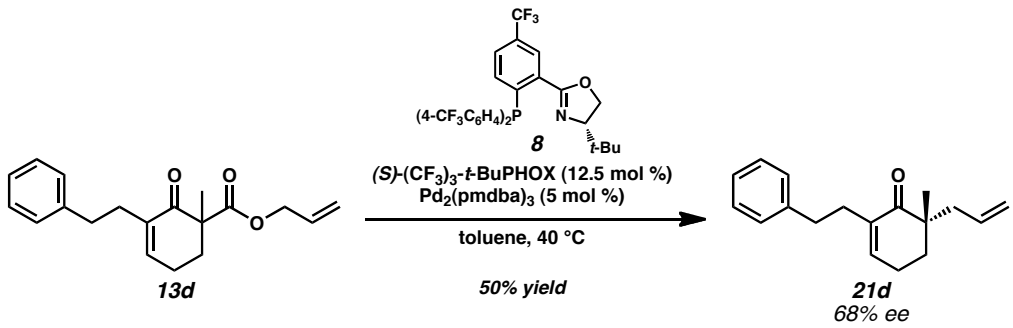
Diosphenol ether 45b. Prepared from **52b**[51] in an analogous manner to **45a**. Purified by flash chromatography (SiO_2, 15 x 3 cm, 20→40% Et_2O in hexanes) to afford diosphenol ether **45b** (57 mg, 0.25 mmol, 27% yield over two steps) as a colorless oil; R_f = 0.54 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96–5.80 (m, 1H), 5.78 (d, *J* = 4.5 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.67–4.55 (m, 2H), 3.60 (s, 3H), 2.56–2.43 (m, 2H), 2.42–2.32 (m, 1H), 1.95–1.85 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 172.2, 150.7, 131.7, 118.4, 115.2, 65.9, 55.2, 54.3, 33.9, 21.5, 20.6; IR (Neat Film NaCl) 2936, 2839, 1734, 1696, 1631, 1455, 1378,

1365, 1252, 1231, 1174, 1110, 1081, 1064, 979, 935, 824 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{17}O_4$ $[M+H]^+$: 225.1121, found 225.1122.

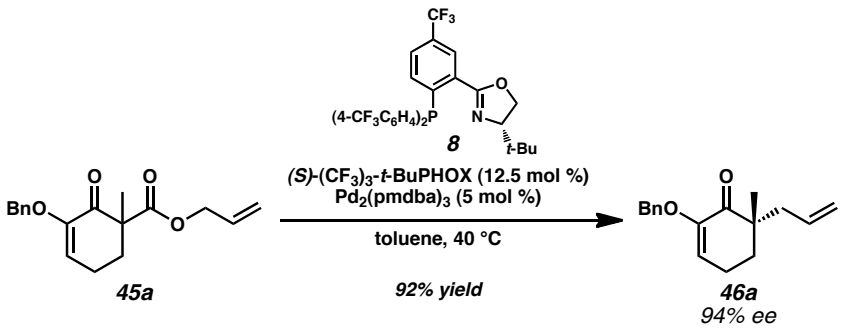
1.4.2.6.11 *Diosphenol Ether and Enone Allylic Alkylation Products*



Enone 21c. Prepared from **13c** in an analogous manner to **46a**. Purified by flash column chromatography (SiO_2, 12 x 2 cm, 10→20% Et_2O in hexanes) to afford enone **21c** (68 mg, 0.28 mmol, 77% yield) as a colorless oil and recovered enone **13c** (19 mg, 18% recovered); R_f = 0.70 (40% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.20 (m, 2H), 7.23 – 7.10 (m, 3H), 6.46 (d, *J* = 4.0 Hz, 1H), 5.75 – 5.60 (m, 1H), 5.08 – 4.93 (m, 2H), 3.50 (dq, *J* = 3.3, 1.6 Hz, 2H), 2.41 – 2.23 (m, 3H), 2.16 (ddt, *J* = 13.7, 7.6, 1.2 Hz, 1H), 1.89 (ddd, *J* = 13.7, 6.4, 5.5 Hz, 1H), 1.74 (ddd, *J* = 13.6, 6.9, 5.5 Hz, 1H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.06 , 144.55 , 140.04 , 137.98 , 134.25 , 129.19 , 128.45 , 126.11 , 118.09 , 44.49 , 41.21 , 36.03 , 33.41 , 23.03 , 21.90; IR (Neat Film NaCl) 3063, 3027, 2964, 2924, 1668, 1640, 1495, 1453, 1430, 1376, 1174, 1077, 996, 915, 749 cm^{-1}; $[\alpha]_D^{25.0}$ –200.23 (c 3.86, $CHCl_3$, 52% ee); HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{21}O$ $[M+H]^+$: 241.1587, found 241.1575; JASCO SFC conditions: 3% MeOH in CO_2, 5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 2.40, minor = 2.11.

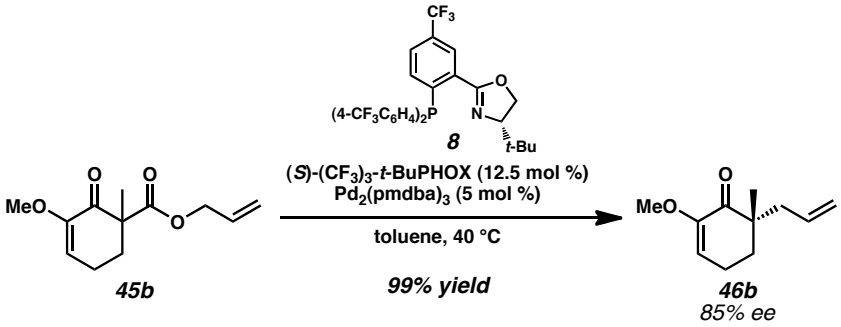


Enone 21d. Prepared from **13d** in an analogous manner to **46a**. Purified by flash column chromatography (SiO_2, 12 x 2 cm, 10→20% Et_2O in hexanes) to afford enone **13c** (17 mg, 67 μmol, 50% yield) as a colorless oil and recovered enone **13d** (8 mg, 20% recovered); R_f = 0.73 (40% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.21 (m, 2H), 7.22–7.13 (m, 3H), 6.50 (t, *J* = 4.1 Hz, 1H), 5.74 (ddt, *J* = 16.8, 10.3, 7.4 Hz, 1H), 5.12–5.00 (m, 2H), 2.76–2.62 (m, 2H), 2.59–2.41 (m, 2H), 2.40–2.12 (m, 4H), 1.89 (ddd, *J* = 13.6, 6.7, 5.5 Hz, 1H), 1.72 (ddd, *J* = 13.6, 6.7, 5.5 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 144.2, 142.1, 137.4, 134.4, 128.7, 128.3, 125.9, 118.1, 44.4, 41.3, 35.2, 33.4, 32.4, 23.0, 22.0; IR (Neat Film NaCl) 3062, 3026, 2962, 2924, 2855, 1669, 1639, 1496, 1453, 1430, 1377, 1175, 1078, 995, 914, 747 cm^{-1}; $[\alpha]_D^{25.0}$ –32.55 (c 1.24, $CHCl_3$, 68% ee); HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{23}O$ $[M+H]^+$: 255.1743, found 255.1730; JASCO SFC conditions: 3% MeOH in CO_2, 5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 2.41, minor = 2.17.



Diosphenol ether 46a. $Pd_2(pmdba)_3$ (4.2 mg, 3.8 μmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 5.7 mg, 9.6 μmol, 12.5 mol %) were added to an oven-dried 2-dram vial equipped with a magnetic stir bar in a glove box. The vial was charged with toluene (1.8 mL) and stirred at ambient temperature (28 °C) for 30 min, resulting in a deep orange solution. β-ketoester **45a** (23 mg, 77 μmol, 1.0 equiv) was transferred to the scintillation vial with toluene (0.5 mL, total = 2.3 mL, 0.033 M), producing a light green solution. The vial was sealed with a Teflon-lined cap and lowered into a heating block (40 °C). After 6 days, the reaction was complete by TLC and colorimetric analysis (the reaction mixture had reverted to an orange color) and was removed from the glove box. The reaction was filtered through a silica gel plug, rinsed with Et_2O, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 15 x 1.5 cm, 5%→10% Et_2O in hexanes) to afford diosphenol ether **46a** (18 mg, 70 μmol, 92% yield) as a colorless oil; R_f = 0.56 (40% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 5.83 (t, *J* = 4.5 Hz, 1H), 5.74 (ddt, *J* = 16.7, 10.3, 7.4 Hz, 1H), 5.12–5.03 (m, 2H), 4.85 (s, 2H), 2.42–2.33 (m, 3H), 2.21 (ddt, *J* = 13.8, 7.6, 1.2 Hz, 1H), 1.89 (ddd, *J* = 13.7, 6.7, 5.6 Hz, 1H), 1.71 (ddd, *J* = 13.7, 6.6, 5.4 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 149.0, 136.8, 134.1, 128.6, 127.9, 127.4, 118.4, 118.0, 70.0, 45.4, 41.2, 33.1, 21.9, 20.9; IR (Neat Film NaCl) 2918, 2360, 1684,

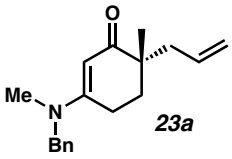
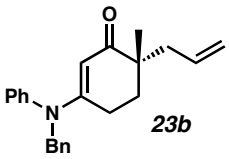
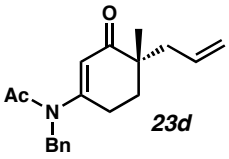
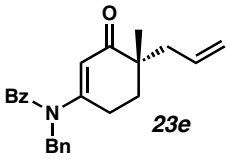
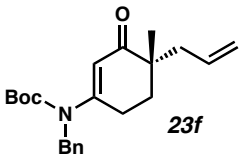
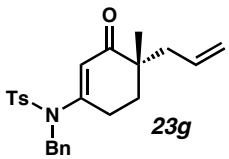
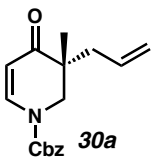
1628, 1457, 1220, 1204, 1094, 1050, 914, 736 cm^{-1}; $[\alpha]_D^{25.0}$ –12.01 (c 0.50, $CHCl_3$, 94% ee); HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{21}O_2$ $[M+H]^+$: 257.1536, found 257.1529; HPLC conditions: 7% IPA in hexanes, 1 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 7.24, minor = 8.27.

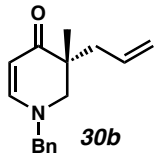
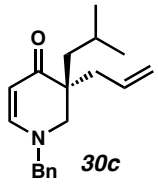
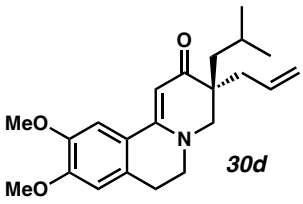
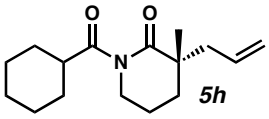
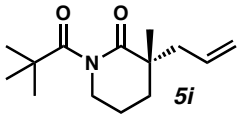
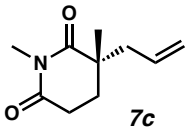
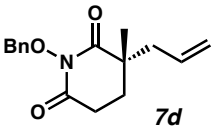
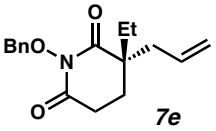


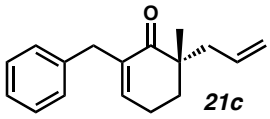
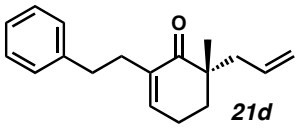
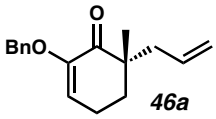
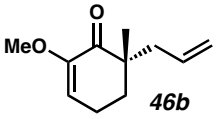
Diosphenol ether 46b. Prepared from **45b** in an analogous manner to **46a**. Purified by flash column chromatography (SiO_2, 10 x 3 cm, 5→10% Et_2O in hexanes) to afford diosphenol ether **45b** (111 mg, 0.616 mmol, 99% yield) as a colorless oil; R_f = 0.23 (40% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.79–5.65 (m, 2H), 5.12–5.01 (m, 2H), 3.58 (s, 3H), 2.47–2.34 (m, 3H), 2.20 (ddt, *J* = 13.7, 7.6, 1.1 Hz, 1H), 1.91 (ddd, *J* = 13.7, 6.8, 5.5 Hz, 1H), 1.72 (ddd, *J* = 13.7, 6.5, 5.4 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 150.0, 134.0, 118.4, 114.5, 55.1, 45.4, 41.2, 33.2, 21.9, 20.8; IR (Neat Film NaCl) 2929, 1687, 1631, 1455, 1375, 1225, 1095, 1056, 913 cm^{-1}; $[\alpha]_D^{25.0}$ –27.47 (c 6.00, $CHCl_3$, 85% ee); HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{17}O_2$ $[M+H]^+$: 181.1223, found 181.1222; HPLC conditions: 2% IPA in hexanes, 1 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 13.41, minor = 12.23.

1.4.2.7 Determination of Enantiomeric Excess

Table 1.5. Methods for the determination of enantiomeric excess (chiral HPLC and SFC).

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 *23a*	SFC Chiralcel OD-H 5% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	10.45	9.60	81
2	 *23b*	SFC Chiralpak AS-H 5% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	8.60	6.48	83
3	 *23d*	SFC Chiralpak AD-H 5% MeOH in CO_2 isocratic, 3.0 mL/min 254 nm	8.45	10.35	86
4	 *23e*	SFC Chiralpak AD-H 7% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	8.04	8.97	87
5	 *23f*	SFC Chiralpak AD-H 7% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	4.04	2.20	82
6	 *23g*	SFC Chiralpak AD-H 10% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	5.60	4.73	84
7	 *30a*	SFC Chiralpak AD-H 10% MeOH in CO_2 isocratic, 3.0 mL/min 254 nm	2.80	3.13	84

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
8	 *30b*	HPLC Chiralcel OJ 10% IPA in hexanes isocratic, 1.0 mL/min 210 nm	18.77	21.21	86
9	 *30c*	HPLC Chiralcel OJ 7% IPA in hexanes isocratic, 1.0 mL/min 210 nm	11.44	14.80	88
10	 *30d*	HPLC Chiralpak AD 30% IPA in hexanes isocratic, 1.0 mL/min 254 nm	21.87	18.59	90
11	 *5h*	SFC Chiralcel OJ-H 1% IPA in CO_2 isocratic, 5.0 mL/min 222 nm	2.53	2.13	95
12	 *5i*	HPLC Chiralcel OD-H 5% IPA in hexanes isocratic, 1.0 mL/min 210 nm	7.95	6.52	96
13	 *7c*	HPLC Chiralpak AD 3% IPA in hexanes isocratic, 1.0 mL/min 210 nm	11.94	17.86	76
14	 *7d*	SFC Chiralcel OJ-H 1% MeOH in CO_2 isocratic, 3.0 mL/min 210 nm	4.03	3.64	96
15	 *7e*	SFC Chiralcel OB-H 1% MeOH in CO_2 isocratic, 2.5 mL/min 210 nm	14.34	13.39	98

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
16	 ***21c***	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	2.40	2.11	52
17	 ***21d***	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	2.41	2.17	68
18	 ***46a***	HPLC Chiralcel OD-H 7% IPA in hexanes isocratic, 1.0 mL/min 254 nm	7.24	8.27	94
19	 ***46b***	HPLC Chiralcel OD-H 2% IPA in hexanes isocratic, 1.0 mL/min 254 nm	13.41	12.23	85

1.5 NOTES AND REFERENCE

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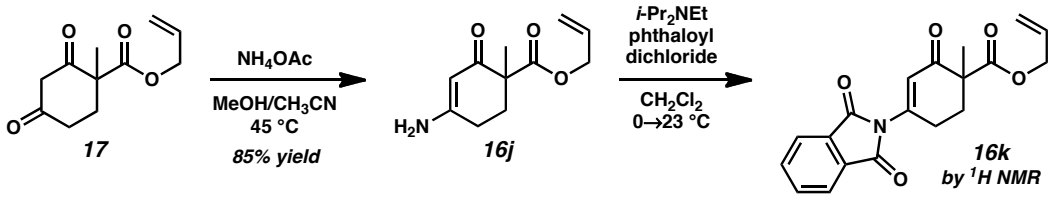
23a). ^{1}H NMR analysis suggests that the product was formed, but enaminone **16k** was not pursued further due to the results of the initial enaminone screen. See: Hansen, K. B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.; Spindler, F.; Malan, C.; Grabowski, E. J. J.; Armstrong, III , J. D. *J. Am. Chem. Soc.* **2009**, *131*, 8798–8804.



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(33) As mentioned previously, the corresponding electron-rich lactams (*N*-substituent = Me or Bn) exhibit little to no conversion to the desired products.

(34) For example, selectivities for lactam **5a** vary from 99% ee with (*S*)-**8** to 86% ee with (*S*)-**3** in toluene and to 96% ee with (*S*)-**8** in THF (Table 1.1).

(35) The distinction between *N*-substituents is most apparent when comparing benzoyl and tosyl lactams, which vary by ~40–80% ee depending on the conditions (see Table 1.1).

(36) Employing optimized conditions with (*S*)-**3** in Et_2O, enone **21a** has been isolated in 90% ee. See ref. 6b.

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(42) Interestingly, both groups found that Trost ligands failed to provide the desired α-quaternary products.

(43) The increase in steric bulk for substrates **4i** and **j** slows the reaction dramatically. Imide **7c** is also hampered by low reactivity. As such, these reactions with these substrates are often not run to completion and consequently have lower yields. See experimental section.

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