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

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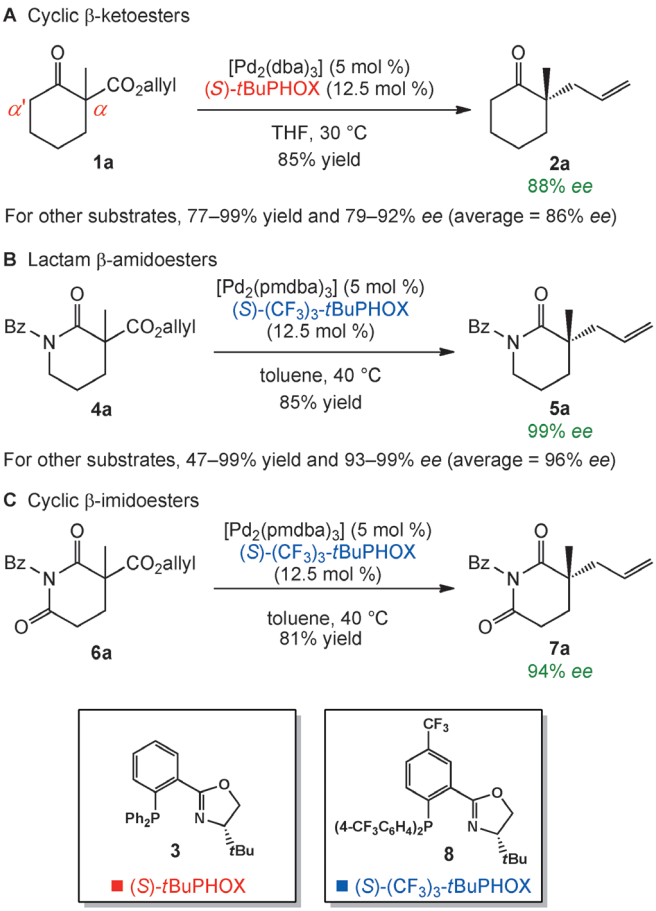
The asymmetric construction of quaternary stereocenters is a topic of great interest in the organic chemistry community. Among the available methods that afford this motif,[1] palladium-catalyzed decarboxylative allylic alkylation[2,3] has proven particularly effective and, over the last decade, our 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 A).[6] Since these early results, we have considerably expanded the scope,[7] demonstrated multiple applications,[8] and performed mechanistic investigations[9] of this powerful 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 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 the 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 to result from a combination of stereoelectronic and steric factors associated with the α′-substituent.

Initially, we hypothesized that the divergence in enolate electronics between the substrate classes depicted in Scheme 1 could be the major determining factor of the observed enantioselectivities. Insight from our previous work[9,10] suggested that differences in selectivity in the alkylation of electron-poor and -rich molecules could be considerable. To investigate the electronic effect of the nitrogen atom on alkylation selectivity without the influence of α′-functionality, we examined variably functionalized enaminones (vinylogous amides such as **12**) as electronic analogues of lactams (**4**, Figure 1). We were particularly drawn to this new class of compounds as our past experience with vinylogous esters **10**[11] and thioesters **11**[11b,12] would provide a foundation and comparison point.[13]



Scheme 1. Comparison of allylic alkylation of ketones, lactams, and imides.

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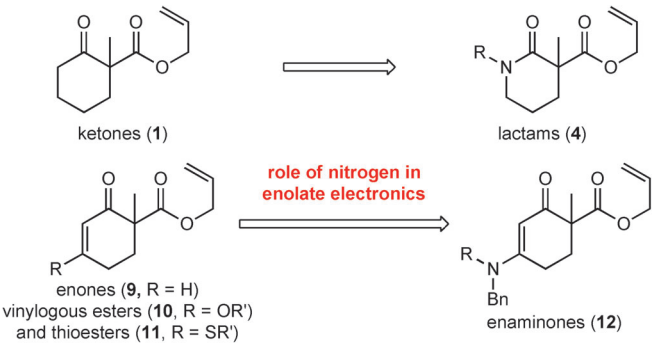


Figure 1. Ketone and lactam enantioselectivity divergence as inspiration for investigation of enolate electronics using vinylogous systems.

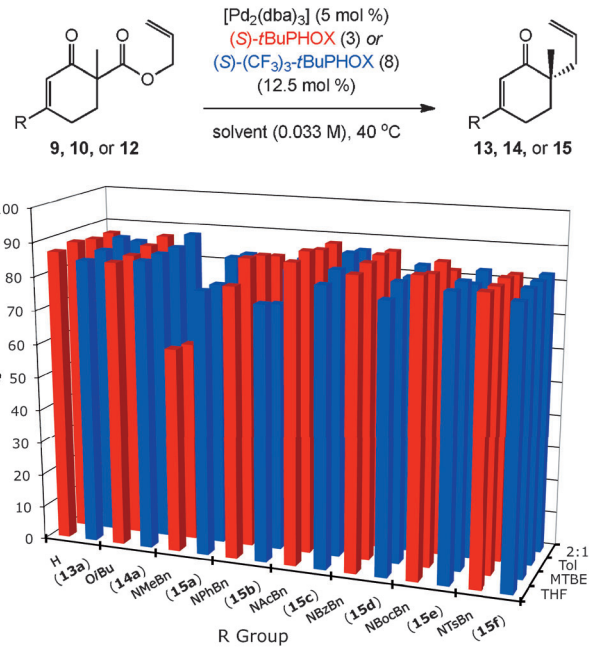
We consequently prepared a number of racemic alkylation precursors and screened these under a series of palladium-catalyzed decarboxylative allylic alkylation conditions (Table 1). This study was performed in a manner similar to our previous investigation of lactams,[10,14,15] employing two electronically differentiated chiral ligands, (*S*)-**3** and (*S*)-**8**, and four solvents of differing polarity: tetrahydrofuran (THF), methyl *tert*-butyl ether (MTBE), toluene, and a mixture of hexane/toluene (2:1).

We made several observations upon analysis of the ligand, solvent, and substrate trends that distinguish 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 (Table 1 entries 7–16), with the exception of methyl enaminone **15a**, which significantly favors (*S*)-**8** (entries 5 and 6). Second, no significant solvent trend is observed for enaminones overall. Third, electron-rich enaminones (i.e., **15a** and **b**) display decreased enantioselectivities and also require extended reaction times for completion,[16] while enaminones bearing electron-withdrawing substituents (**15c–f**) are all generated in 80–90% enantiomeric excess (*ee*). By comparison, lactam substrates perform with much higher enantioselectivity with ligand (*S*)-**8** in nonpolar solvents.[10,17] Furthermore, the modest differences in enantioselectivity for the electron-withdrawing enaminones sharply contrasts with the corresponding lactam series, in which the N-substituent plays a considerable role, producing significant variation in selectivity.[10,18] 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 reaction screening is that enantioselectivities observed for enaminones **15c–f** are approximately equivalent to results obtained for enone **13a**,[19] vinylogous ester **14a**, and even more general ketone substrates. Of all the enaminones screened, acetyl variant **15c** provides the highest selectivity at 90% *ee* in MTBE, which is only marginally better than the optimal values for the related vinylogous systems. The modest differences between these vinylogous molecules (i.e., **13–15**) further suggests that the electronic nature of the enolate is not likely the predominant factor in providing high enantioselectivity for lactams and imides.

While pursuing enaminones, we also briefly examined the related 2,3-dihydropyridin-4-ones, which possess a nitrogen atom within the ring (Table 2). *N*-Carboxybenzyl-substituted

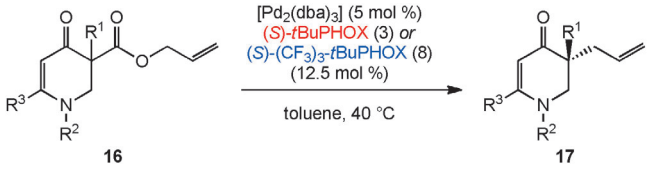
Table 1. Enaminone allylic alkylation screen.[a]

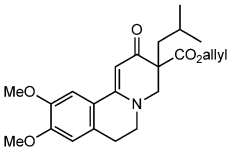


	Substrate	R	Product	Ligand	Enantiomeric excess [% *ee*][b] THF	MTBE	Toluene	Hexane/ Toluene (2:1)
1	**9a**	H	**13a**	**3**	87	88	87	87
2				**8**	85	86	88	85
3	**10a**	O*i*Bu	**14a**	**3**	85	85	86	87
4				**8**	86	86	86	88
5	**12a**	NMe(Bn)	**15a**	**3**	61	60	55	52
6				**8**	79	78	84	83
7	**12b**	NPh(Bn)	**15b**	**3**	81	87	85	83
8				**8**	76	74	82	83
9	**12c**	NAc(Bn)	**15c**	**3**	89	90	88	88
10				**8**	83	85	88	86
11	**12d**	NBz(Bn)	**15d**	**3**	86	87	88	87
12				**8**	80	83	82	83
13	**12e**	NBoc(Bn)	**15e**	**3**	87	86	87	82
14				**8**	84	84	81	83
15	**12f**	NTs(Bn)	**15f**	**3**	84	83	83	82
16				**8**	82	83	83	83

[a] Conditions: enone **9a**, vinylogous ester **10a**, or enaminone **12a–f** (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 supercritical fluid chromatography (SFC) with chiral stationary phase. Red = with (*S*)-**3** as ligand and blue = with (*S*)-**8** as ligand.

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

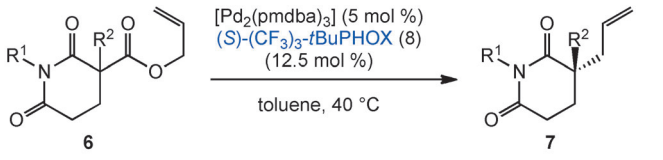


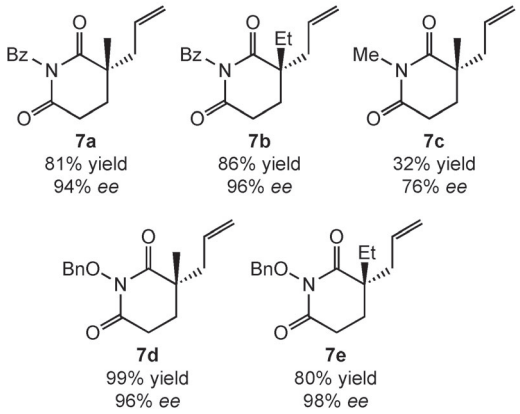
	Substrate	R^1	R^2	R^3	Product	Ligand	Yield [%]	*ee* [%][b]
1	**16a**	Me	Cbz	H	**17a**	**3**	80	86
2						**8**	98	84
3	**16b**	Me	Bn	H	**17b**	**3**	82	88
4						**8**	94	86
5	**16c**	*i*Bu	Bn	H	**17c**	**3**	85	84
6						**8**	81	88
7	**16d**				**17d**	**8**	81	91

[a] Conditions: 2,3-dihydropyridin-4-ones **16**, $[Pd_2(dba)_3]$ (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 chiral HPLC or SFC. Red = with (*S*)-**3** as ligand and blue = with (*S*)-**8** as ligand.

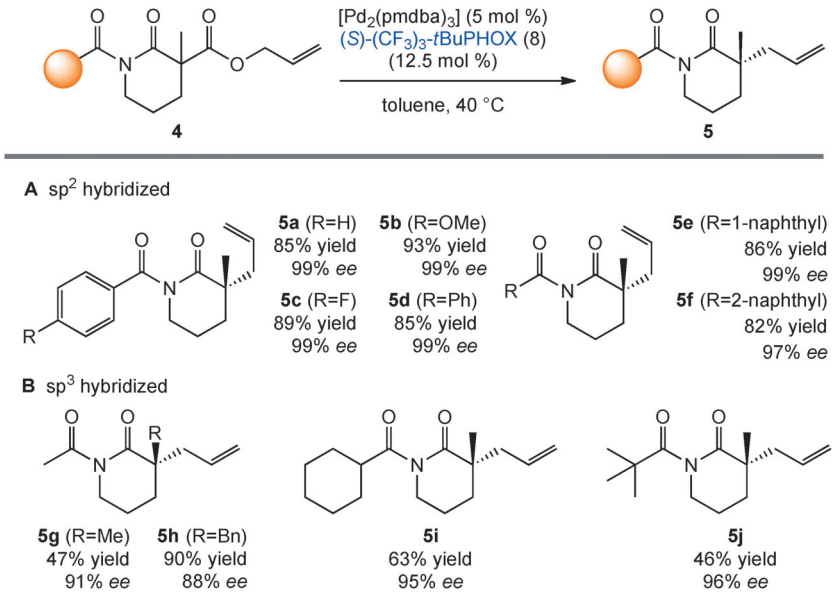
product **17a** is formed with enantioselectivities similar to electronically related enaminones, and electron-rich 2,3-dihydropyridin-4-ones **17b** and **c** are curiously also generated in the same range. Even 2,3-dihydropyridin-4-one **17d** is produced in good enantioselectivity, despite the highly electron-rich nature of the enolate. These results again allude to other factors beyond enolate electronics that direct alkylation selectivity.

Having investigated the impact of enolate electronics, we diverted our efforts to study the influence of α′-functionality on alkylation selectivity (Scheme 2). Our previous lactam screen identified the benzoyl moiety as the optimal protecting group,[10] providing high to near-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**) also display excellent *ee* values, 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 proceeded with improved enantioselectivities compared with analogous





Scheme 3. Allylic alkylation of cyclic imides.



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

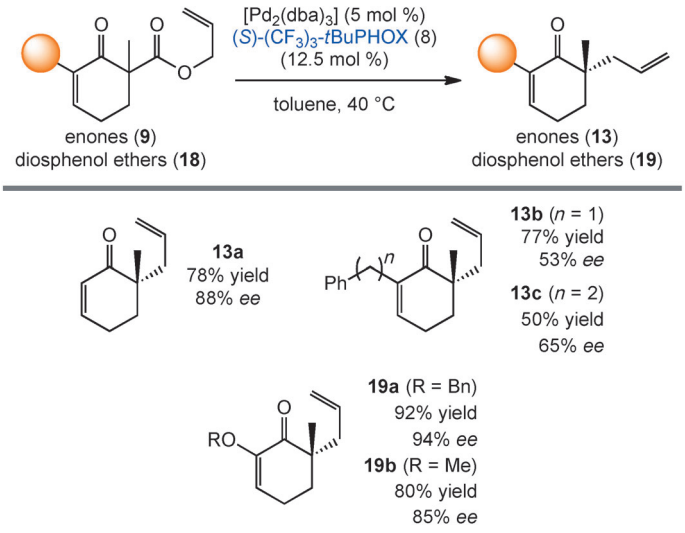
acetyl lactam **4g**, supporting a steric effect.[20]

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 3). However, we observed that formation of *N*-methyl imide **7c** proceeds with moderate enantioselectivity and is hampered by low reactivity. As this substrate also generates an intermediate imido enolate (as do lactams **5a–j**, Scheme 2), 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.

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.

To examine the relative influence of the steric and stereoelectronic effects associated with the α′-group, we prepared enones **9b** and **c** and diosphenol ethers **18a** and **b** and subjected these substrates to the standard conditions employed in the alkylation of lactams and imides (Scheme 4). Enones



Scheme 4. Allylic alkylation of α′-functionalized enones.

13b and **c** are formed in low enantioselectivity. By contrast, benzyl diosphenol ether **19a**, which differs from **13c** 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 to be critical in obtaining high enantioselectivity, as methyl diosphenol ether **19b** is produced in 85% *ee*. In comparison, analogous enone **9a**, which bears no α′-functionality, proceeds under the same conditions to afford enone **13a** in 88% *ee*,[19] 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 **18a**, which proceeds with the greatest enantioselectivity observed in a Pd(PHOX) catalyst system for a carbocyclic substrate bearing an α-methyl group and unsubstituted allyl moiety.

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.

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Keywords: allylation · asymmetric catalysis · heterocyclic compounds · high-throughput screening · palladium

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[12] For examples of research on vinylogous thioesters, see: a) S. R. Levine, M. R. Krout, B. M. Stoltz, *Org. Lett.* **2009**, *11*, 289–292; b) K. V. Petrova, J. T. Mohr, B. M. Stoltz, *Org. Lett.* **2009**, *11*, 293–295.

[13] Concurrent with our efforts, Trost has also performed palladium-catalyzed asymmetric allylic alkylations to form enantioenriched α-quaternary vinylogous esters and thioesters. See: a) B. M. Trost, C. Pissot-Soldermann, I. Chen, G. M. Schroeder, *J. Am. Chem. Soc.* **2004**, *126*, 4480–4481; b) B. M. Trost, G. M. Schroeder, *Chem. Eur. J.* **2005**, *11*, 174–184; c) B. M. Trost, C. Pissot-Soldermann, I. Chen, *Chem. Eur. J.* **2005**, *11*, 951–959; d) B. M. Trost, R. N. Bream, J. Xu, *Angew. Chem.* **2006**, *118*, 3181–3184; *Angew. Chem. Int. Ed.* **2006**, *45*, 3109–3112.

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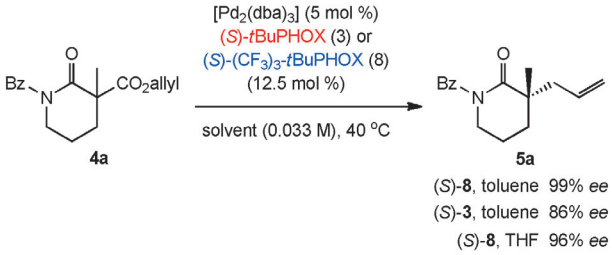
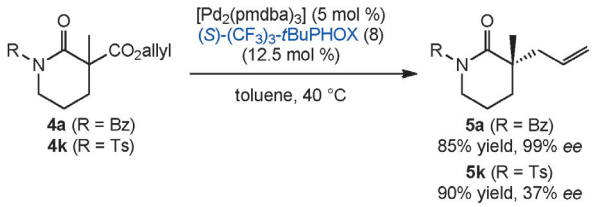
[15] See Supporting Information.

[16] Corresponding electron-rich lactams (N-substituent = Me or Bn) exhibit little to no conversion to the desired products and, as such, are poor alkylation substrates.

[17] 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.



[18] For example, with (*S*)-**8** in toluene, observed selectivities for lactams vary from 99% *ee* (**5a**, R = Bz) to 37% *ee* (**5b**, R = Ts).



[19] Employing optimized conditions with (*S*)-**3** in Et_2O, enone **13a** has been isolated in 90% *ee*. See ref. [6b].

[20] The increase in steric bulk for substrates **4i–j** also slows the reaction dramatically. See Supporting Information.

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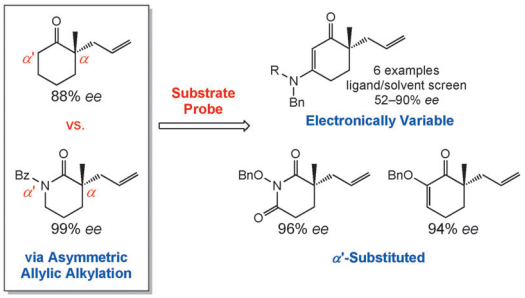
Stereoselective Catalysis

*N. B. Bennett, D. C. Duquette, J. Kim, W.-B. Liu, A. N. Marziale, D. C. Behenna, S. C. Virgil, B. M. Stoltz** ..... ▮▮▮▮–▮▮▮▮

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



Eeny, meeny, miny … enaminones! Lactams and imides have been shown to consistently provide enantioselectivities substantially higher than other substrate classes previously investigated in the palladium-catalyzed asymmetric decarboxylative allylic alkylation. Several new substrates have been designed to probe the contributions of electronic, steric, and stereoelectronic factors that distinguish the lactam/imide series as superior alkylation substrates (see scheme). These studies culminated in marked improvements on carbocyclic allylic alkylation substrates.

