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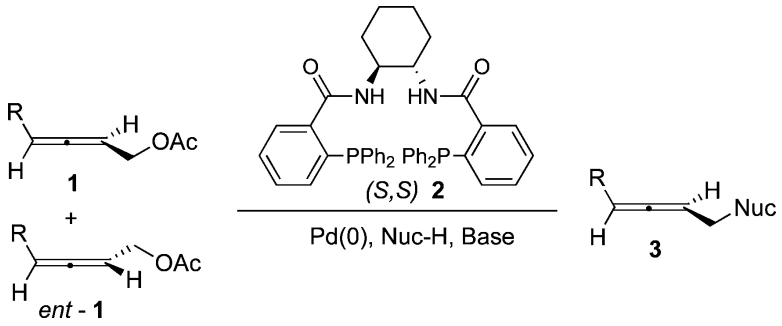

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Dynamic Kinetic Asymmetric Allylic Alkylations of Allenes

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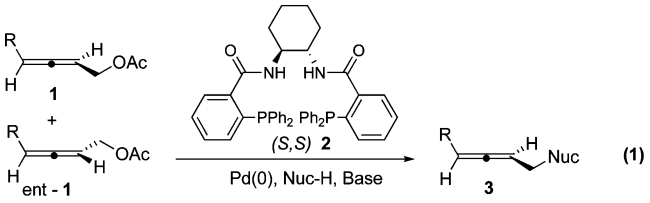
Efficient and atom economic[1] methods for construction of chiral allenes are of significance due to the presence of this core structure in numerous natural and biologically important products,[2] as well as synthetic intermediates for asymmetric synthesis of targets involving chirality transfer.[2,3] Undoubtedly, the potential in this latter regard has been retarded by the limited accessibility of enantioenriched allenes. Typically, chiral allenes are derived from chiral propargylic alcohols.[2,4] Only recently has asymmetric catalysis been employed for the construction of allenes.[2,5] Several limited methods utilize the asymmetric addition of soft nucleophiles to vinyl−allyl Pd(II) intermediates accessed through both the oxidative addition of racemic 2,3-alkadienyl phosphates[6] and prochiral vinyl bromides.[7] Our group has been active in related palladium-catalyzed asymmetric allylic alkylations (AAA) through a dynamic kinetic asymmetric transformation (DYKAT) utilizing our ligands.[8] Therefore, we focused our studies on the use of these ligands for the dynamic kinetic asymmetric addition of nucleophiles to allenes (eq 1), which has led to a general access to allenes of high enantiomeric excess for both carbon- and nitrogen-based nucleophiles. Further, a most unusual dependence of enantioselectivity on base in the case of amine nucleophiles has been uncovered.



(1)

Optimization of the ligand, solvent, palladium precatalyst, and additive revealed the standard catalyst system as $Pd_2dba_3-CHCl_3$ (2.5 mol %), ligand **2** (7.5 mol %), and THACl (tetrahexylammonium chloride) (5 mol %) in THF. Asymmetric addition of diethyl methylmalonate to allene **4** with lithium diisopropylamide (LDA) afforded allene **10** in 90% yield and 85% ee. THACl as a catalytic additive provided an incremental but consistent increase in enantioselectivity with THF as the solvent. Unlike previous Pd-catalyzed asymmetric allylic alkylations using these ligands,[11] bases with a more coordinating and smaller countercation (entries 1 and 2) provided the highest enantioselectivity (Table 1).[12]

After establishing the optimized conditions, the scope and limitation of the dynamic kinetic asymmetric addition of malonates to allene acetates was explored (Table 2). Increasing the size of the allene substituent only slightly increased the enantiomeric excess (entries 1−4). Unsubstituted malonates also afford high enantioselectivity (86% ee) by employing a 3-fold excess of the malonate to suppress bisalkylation (entry 5). Most importantly, these conditions tolerate additional functionality, such as dienes, to provide chiral precursors suitable for further transformations (entries 6 and 7).

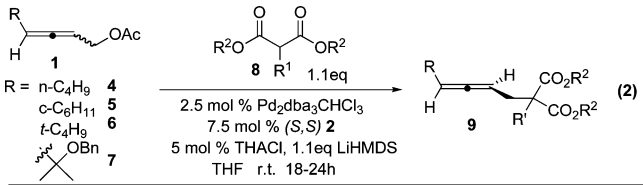
The dynamic kinetic asymmetric addition of amines to allenes further demonstrates the profound influence of the base on the enantioselectivity (Table 3). Chiral (*S*)-(+)-allenamines **19**−**21** were prepared with high enantioselectivities (89−95% ee) by employing 1.1 equiv of the amine and an excess of Cs_2CO_3 (entries 1−3, 5).

Table 1. Base Effect on the Dynamic Kinetic Asymmetric Alkylation of Allene **4** with Diethyl Methylmalonate[a]

entry	base	ee (%)[b]	yield (%)[c]
1	LDA	85	90
2	LiHMDS	84	84
3	KHMDS	45	84
4	NaH	75	70
5	Cs_2CO_3	23	46
6	*c*-$C_6H_{11}MgCl$		NR
7	KHMDS/$ZnCl_2$		NR
8[d]	BSA/5% KOAc	45	47
9	KHMDS/Et_3B	48	92
10	KHMDS/$(EtO)_3B$	48	85

[a] Reaction performed with $Pd_2dba_3CHCl_3$ (2.5 mol %), (*S*,*S*)-**2** (7.5 mol %), allene/malonate/base (1/1.1/1.1) in THF at room temperature. [b] Determined by chiral HPLC. [c] Isolated yield of allene (*S*)-(+)-**10**. NR = no reaction. BSA= *N*,*O*-bis(trimethylsilyl)acetamide. [d] From ref 9.

Table 2. Dynamic Kinetic Asymmetric Alkylation of Allenes with Malonates[a]



(2)

entry	*allene*	R^1	R^2	*Product*[a]	*ee*[b] *(yield)*[c]
1	**4**	Me	Et	*(S)*-(+)-**10**	86% *(85%)*
2	**5**	Me	Et	*(S)*-(+)-**11**	90% *(87%)*
3	**6**	Me	Et	*(S)*-(+)-**12**	89% *(89%)*
4	**7**	Me	Et	*(S)*-(+)-**13**	91% *(95%)*
5[d]	**7**	H	Me	*(S)*-(+)-**14**	86% *(63%)*
6	**4**	Sorbyl	Me	*(S)*-(+)-**15**	87% *(74%)*
7	**7**	Sorbyl	Me	*(S)*-(+)-**16**	90% *(97%)*

[a] Absolute configuration determined by comparison to (*S*)-(+)-**10** with known stereochemistry derived from D-mannitol, analogy, and the Lowe−Brewster rule.[10] [b] Enantiomeric excess determined by chiral HPLC. [c] Isolated yields. [d] With 3 equiv of malonate employed. Sorbyl = *trans*,*trans* 2,3-hexadienyl.

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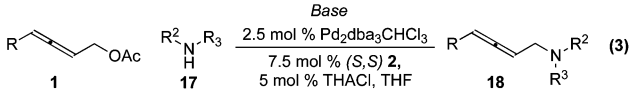
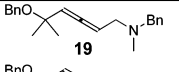
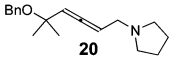
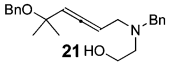
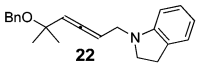
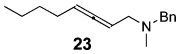
Table 3. Dynamic Kinetic Asymmetric Alkylation of Allenes with Amines



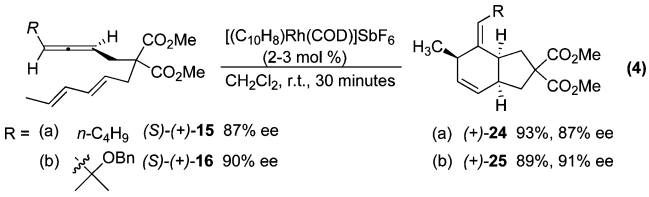
entry	*Product*	*Condition*[a]	*ee*[b] *(Config)*[c]	*yield*[d]
1	 **19**	**A**	95% (S)-(+)	98%
		B	65% (R)-(-)	91%
2	 **20**	**A**	89% (S)-(+)	86%
		B	28% (R)-(-)	90%
3[e]	 **21**	**A**	90% (S)-(+)	89%
		B	35% (R)-(-)	85%
4	 **22**	**C**	84% (R)-(-)	88%
5	 **23**	**A**[f]	~90% (S)-(+)[g]	56%

[a] Conditions: **A**. 1.1 equiv of amine to allene, 3 equiv of Cs_2CO_3, room temperature, 1 day. **B**. 2.2 equiv of amine to allene, room temperature, 1 day. **C**. 1.1 equiv of indoline to allene, 60 °C, 1 day. [b] Enantiomeric excess determined by chiral HPLC. [c] Absolute configuration determined by comparison of allene (*S*)-(+)-**23** with known stereochemistry derived from D-mannitol, analogy, and Lowe−Brewster rule.[10] Reversal in stereochemistry was verified by both chiral HPLC and optical rotation. [d] Isolated yield. [e] Reaction performed at 60 °C for 18 h. [f] Reaction conducted with Pd_2dba_3−$CHCl_3$ (7.5 mol %), (*S*,*S*)-**2** (22.5 mol %), THACl (15 mol %). [g] Enantiomeric excess (±10%) determined by optical rotation compared to material with known enantiomeric excess.[13]

Interestingly, the utilization of the identical (*S*,*S*) catalyst system and a 2-fold excess of the amine resulted in the formation of the opposite enantiomer (*R*) with lower enantiomeric excess (28−65% ee). Indoline did not require a base and provided the DYKAT adduct with a slight decrease in selectivity (entry 4). The asymmetric addition of *N*-benzylmethylamine to allene **4** proceeded with only partial conversion with 2.5 mol % of palladium dimer. Attributing this difference in reactivity to product inhibition, tripling the standard catalyst loading enabled complete conversion to the product allenamine **23** (entry 5).[13]

In general, for a Pd-catalyzed AAA involving a DYKAT, one must establish Curtin−Hammett conditions and promote a selective nucleophilic addition to one diastereomeric π-allyl Pd(II) intermediate over the other. The reasonable effect of THACl[8] and dba (dibenzylideneacetone)[7b] as additives on the enantioselectivity is due to increasing the rate of such an interconversion. Unlike previous AAA of allenes with malonate nucleophiles,[6,7] the above conditions afforded high enantioselectivities for allenes, regardless of the size of the allene substituent ranging from 86% ee for *n*-butyl to 91% ee for a tertiary group. Furthermore, the dramatic reversal in enantioselectivity in the addition of amines to allenes demonstrates the choice of the base in addition to the chirality of the ligand determines which diastereomeric π-allyl Pd(II) intermediate is preferentially attacked and hence the chirality of the product. In addition to obtaining a Curtin−Hammett situation, conditions must be optimized to favor a selective nucleophilic attack to one diastereomeric π-allyl Pd(II) intermediate. This observation may also explain the base effect on the malonate cases, but its effect purely on the rate of the interconversion cannot be discredited since no reversal in asymmetric induction was observed.

The utility of this developed methodology can be demonstrated by the formal intramolecular Diels−Alder reaction of the DYKAT products **15** and **16**.[2,3,14] Allenes **15** and **16** were unreactive to the reported conditions for the intramolecular [4 + 2] cycloaddition of 1,1-disubstituted allenes to dienes under catalysis by $[Rh(COD)Cl]_2$ and P(O-*o*-BiPh)$_3$.[15] On the other hand, employment of a catalyst[16] shown to be more active in other types of cycloadditions efficiently provided the cycloisomers with complete chirality transfer and as one diastereomer (eq 4).



In conclusion, we have developed highly enantioselective conditions for the dynamic kinetic asymmetric allylic alkylation of racemic allenes with amines and malonates and demonstrated a dramatic base effect. Furthermore, these DYKAT products are well suited for further useful transformations wherein the axial chirality is faithfully transferred into multiple stereogenic centers as well as olefin geometry.

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Supporting Information Available: Synthesis of the allene substrates, experimental details, establishment of the absolute configurations, and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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