A Pd–H/Isothiourea Cooperative Catalysis Approach to anti-Aldol Motifs: Enantioselective α-Alkylation of Esters with Oxyallenes

Hua-Chen Lin, Gary J. Knox, Colin M. Pearson, Veronica Carta and Thomas N. Snaddon*[a]

Department of Chemistry, Indiana University, 800 E. Kirkwood Ave., Bloomington, IN 47401, USA

Abstract. The biological and therapeutic significance of polyketides is a powerful impetus for the development of efficient methods to facilitate their construction. Emulating the efficiency of polyketide biosynthesis, a sophisticated arsenal of aldol-based strategies has evolved that is contingent on the generation of single enolate isomers. Since this has the potential to compromise efficiency in reagent-based paradigms, direct catalysis-based solutions would be enabling. To complement the array of substrate-based strategies, and regulate enolate geometry at the catalyst level, a direct catalytic alkylation of esters with oxyallenes has been developed. Synergizing metal hydride reactivity with Lewis base catalysis has resulted in a broad reaction scope with useful levels of stereocontrol (up to >99% *ee*). Facile derivatization of these ambiphilic linchpins is demonstrated, providing access to high-value *vicinal* stereocenter-containing motifs, including 1,2-amino alcohols.

Main Text. Metal hydrides (M–H) manifest themselves in all facets of the contemporary catalysis spectrum.[1] The success of these intermediates reflects their versatile reactivity profile which, in turn, can be modulated through judicious choice of the metal and/or the supporting ligands. Despite the steep trajectory of advances in this arena, strategically leveraging π-bond activation by M–H species in conjunction with Lewis base catalysis within the framework of enantioselective cooperative catalysis remains conspicuously underdeveloped.[2] Our interest in combining transition metal- and Lewis base organocatalysis[3-5] presented an opportunity to reconcile this disparity and in so doing unveil new avenues to expedite the synthesis of motifs that are common to an array of bioactive molecules such as polyketides. Established aldol preparations typically proceed via the same general template in which enolates (or enolate equivalents) react with aldehyde electrophiles (Figure 1a).[6] Based on this a range of Mukaiyama-type aldol reactions catalyzed by Lewis acids are now available.[7] While these continue to be exceptionally successful approaches that avoid the trapping of carbonyl electrophiles by independently and selectively prepared stereodefined enolates have emerged.[8] Cognizant of these challenges, we envisioned the preparation of enantioenriched aldol products via the *direct* enantioselective alkylation of acyclic esters with oxyallenes[9] in a manner that is complementary to established approaches and facilitates access to high value ambiphilic C5 linchpins that can be functionalized in a bidirectional manner (Figure 1b).

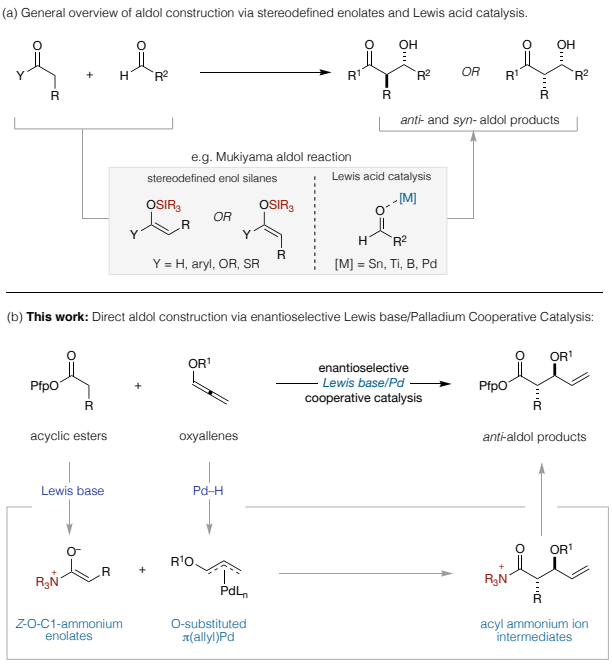
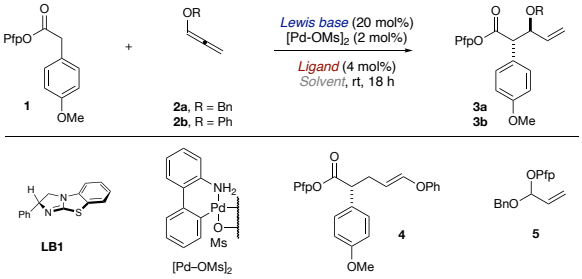


Figure 1. (a) General depiction of aldol construction. (b) This work: enantioselective alkylation of acyclic esters with oxyallenes via cooperative catalysis.

We envisioned a cooperative isothiourea Lewis base–Pd catalyzed process that proceeds via the stereoselective union of (Z)-O-C1-ammonium enolate and O-substituted π(allyl)Pd intermediates (Figure 1b), wherein the requisite O-substituted π(allyl)Pd species would arise by hydropalladation of the oxyallene by a transient hydrido-palladium (Pd–H). If successful, such a scenario would address the issue of enolate geometry and proceed via a non-enolizable electrophilic species. In support of this proposal the Pd-catalyzed alkylation of a limited range of carbon nucleophiles with alkoxyallenes, which proceed via putative Pd–H intermediates, have been reported.[10]

As an entry point for our investigation, we began by evaluating the alkylation of pentafluorophenyl (Pfp) ester **1** with benzyloxyallene **2a** in THF and in the presence of both benzotetramisole **LB1**,[11.12] $[Pd\text{-}OMs]_2$ and Xantphos (**L1**) (Table 1). The *O*-benzyl aldol product **3** was obtained in 80% yield as the *anti*-diastereoisomer (2.5:1 dr) in 98:2 er (Entry 1). The corresponding linear product **4** was barely detectable with the remainder of the mass balance comprising mixed acetal **5**, which was obtained 13% yield. We presumed this to arise from attack of liberated pentafluophenolate upon a likely p(allyl)Pd^+ intermediate.[13] We then moved to evaluate the effect of solvent on both the efficiency and stereoselectivity of the reaction (Entries 2-6) which revealed that competing hemi-acetal by-product **5** was hardly obtained in toluene. Thereafter, and cognizant of the critical effect that bis-phosphine ligand parameters have on both Pd–H reactivity and hydricity,[1b,14] as well as the reactivity, regioselectivity and *syn*/*anti* population of p(allyl)Pd species, we sought to evaluate the effect of the supporting ligand on palladium. Accordingly, we evaluated common bis-phosphine ligands in order of decreasing natural bite angle.[15] DPEphos **L2** (Entry 17, 104°) and DPPF **L3** (Entry 8, 99°) resulted in the same high yields and enantioselectivities but with increased diastereoselectivity (3.2:1 dr and 3.6:1 dr, respectively); however, BINAP **L4** was ineffective[16] (Entry 9, 93°), as were the smaller bite angle aliphatic bisphosphines DPPP **L5** (91°) and DPPE **L6** (86°) (Entries 10 & 11, respectively). Finally, we also surveyed Trost's chiral bidentate DACH-Ph **L7**, a privileged ligand in Pd-catalyzed allylic alkylation,[17] but this was also ineffective (Entry 18-12).[16] Finally, common monophosphine ligands were similarly ineffective and did not result in active catalysts (see Supporting Information). Having completed our ligand assessment and having identified dppf as the most effective we

then confirmed the identical performance of Buchwald's stable and convenient 3rd generation pre-catalyst **G3L3**,[18] which we used subsequently. (Entry **13**). We then evaluated three other common isothiourea Lewis base catalysts (**LB2**–**LB4**, Entries 14–16) in combination with **G3L3**; however, none outperformed BTM **LB1** (Entry 13). At this juncture and based on our previous observations in isothiourea/palladium catalysis, we expected that the observed diastereoselectivity (ca. 3.6:1, *anti*/*syn*, Entry 13) derived from C1-ammonium enolate alkylation by isomeric *syn*- and *anti*-π(allyl)Pd intermediates.[5d,e] As, in addition to ligand effects, both substrate steric and electronic factors have been observed to influence the relative populations of these two isomers,[19] we elected to evaluate and compare phenyoxyallene **2b** as we expected the intermediate OPh-substituted π(allyl)Pd$^+$ intermediate would further favor the *syn*-configuration due to increased conjugation and/or increased steric discrimination. Indeed, phenoxyallene **2b** gave aldol product **3b** in 90% yield and much improved 9.5:1 dr without compromising the level of enantioselectivity.



Entry[a]	oxyallene	Lewis base	Ligand (bite angle)	Solvent	Yield **3** [%][b]	dr[c]	*ee* [%][d]
1	**2a**	**LB1**	**L1**, Xantphos (108°)	THF	80 (13)	2.5:1	94
2				Et_2O	70 (16)	2.3:1	81
3				1,4-dioxane	53 (9)	2.3:1	96
4				$PhCH_3$	87 (4)	2.5:1	96
5				CH_2Cl_2	77 (13)	1.2:1	48
6				MeCN	79 (11)	1.1:1	30
7			**L2**, DPEphos (104°)	$PhCH_3$	86 (7)	3.2:1	97
8			**L3**, dppf (99°)		86 (6)	3.6:1	96
9			**L4**, (*R*)-BINAP (93°)		--	--	--
10			**L5**, dppp (91°)		--	--	--
11			**L6**, dppe (86°)		--	--	--
12			**L7**, (*S*,*S*)-DACH-Ph		--	--	--
13			**G3L3**, (dppf)PdG3		86 (6)	3.6:1	96
14[e]		**LB2**			21 (13)	2.0:1	–85
15		**LB3**			83 (15)	3.4:1	88
16		**LB4**			87 (8)	1.3:1	20
17	**2b**	**LB1**			90	9.5:1	99

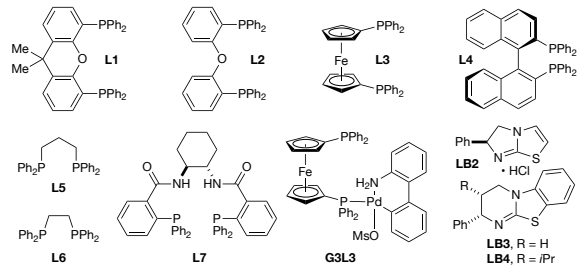
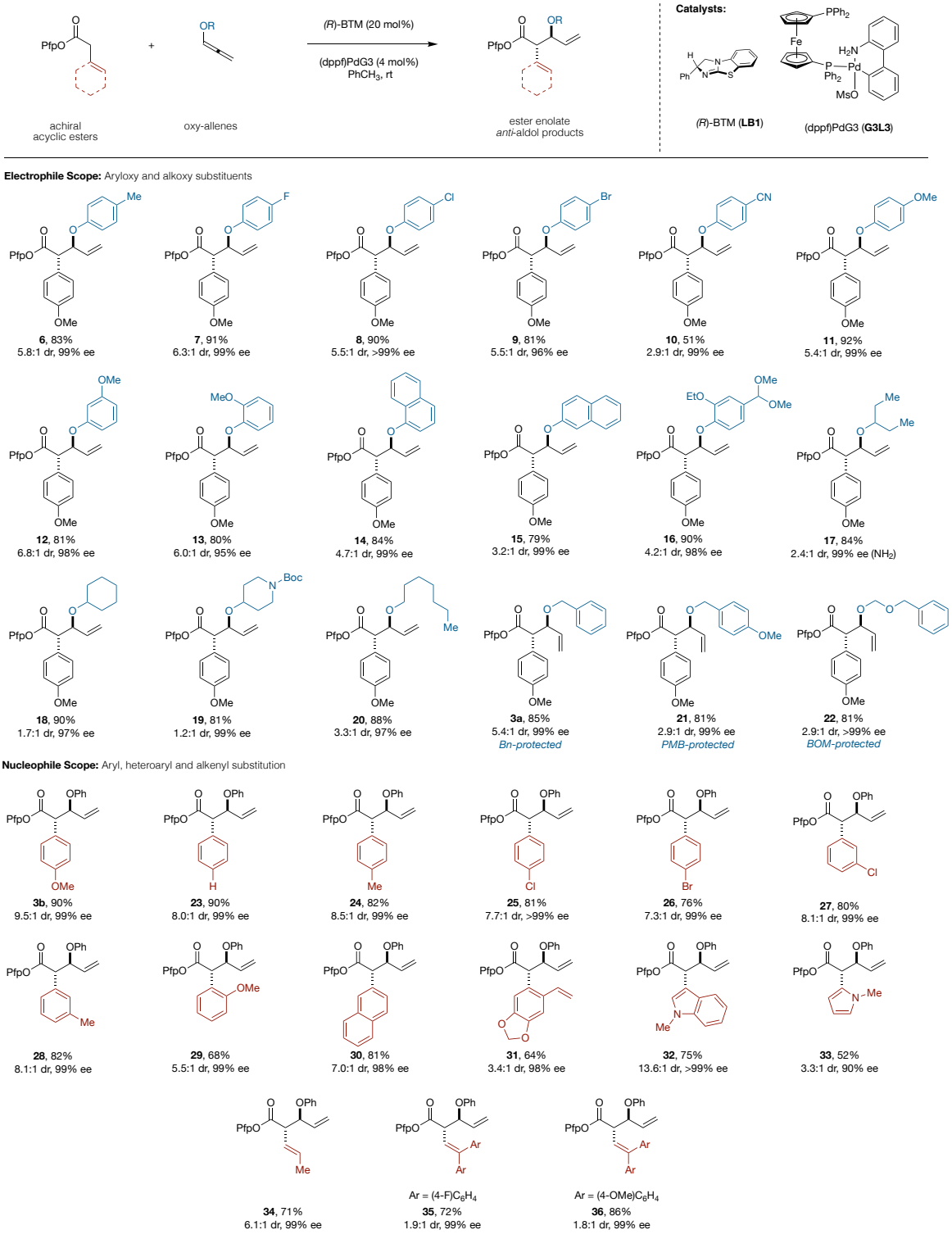


Table 1. Reaction development and Optimization.

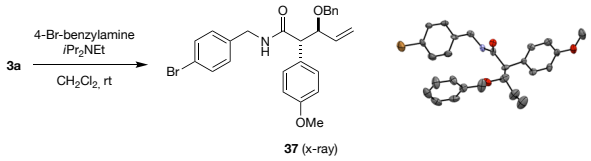
With optimized conditions established and having identified the critical influence of the O-substituent on the diastereoselectivity of the alkylation reaction, we next moved to evaluate the scope of the oxyallene partner more widely. As shown in Scheme 1, various aryloxyallenes reacted with ester **1** under the optimized conditions and provided *anti*-aldol products in high yields, with excellent levels of enantiocontrol and with good levels of diastereoselectivity. There appears to be little sensitivity to changes in the electronics of the arene; in addition to simple methyl substitution (**6**), fluoro (**7**), chloro (**8**) and bromo (**9**) substituents are all tolerated and remain unaltered during the reaction. Comparing electron-withdrawing and electron-donating substituents via *p*-nitrile (**10**) and *p*-methoxy (**11**), respectively, indicated that the former functions with slightly lower levels of efficiency and diastereocontrol. We then interrogated both the electronic and steric effect of the methoxy substituents via the corresponding *m*-methoxy (**12**) and *o*-methoxy (**13**) isomers, which participated with slightly enhanced levels of diastereocontrol. In the case of isomeric and 1- and 2-naphthyloxyallenes (**14** and **15**, respectively) both reacted in similar yield but with enhanced levels of diastereocontrol in the case of **14**. Finally, more complex acetal-containing aryloxyallene gave **16** in with comparable efficiency. Thereafter, we proceeded to evaluate the scope of alkoxyallenes; both acyclic and cyclic aliphatic substitutes gave alkylated products in high yields and enantioselectivities, albeit with lower levels of diastereocontrol relative to the aryloxyallenes. Acyclic alkyl allenyl ethers (**17** & **20**) gave higher levels of *anti*-selectivity than the corresponding cyclic cyclohexyl and *N*-Boc piperidinyl congeners (**18** & **19**, respectively). Finally, we established that PMB (**21**) and BOM-protected (**22**) products could be produced that, in in combination with Bn-protected product (**3a**), provide complementary opportunities for downstream deprotection. Noteworthy is the continued tolerance toward halides (**25**–**27**), as well as tolerance of *o*-substituted arenes (**29** & **31**), indoles (**32**), pyrroles (**33**), and alkenyl substrates.



Scheme 1. Ester and oxyallene substrate scope.

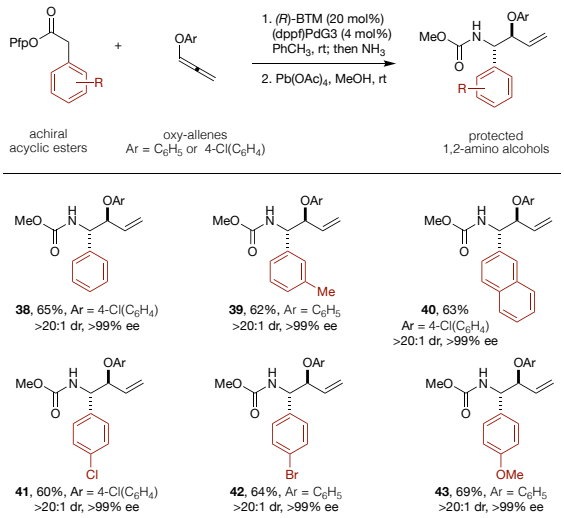
The absolute and relative stereochemical features of the products were confirmed via single crystal x-ray analysis of **37**,[20] the *p*-Br-benzylamide of **3a**, which crystalizes in the rare space group P1 with four

symmetry-independent molecules in the asymmetric unit (Z´=4) (Scheme 2). Further information concerning the structural characterization of compound **37** is available in the Supporting Information.



Scheme 2. Preparation and X-ray Analysis of **37**.

Having assessed the scope of this enantioselective alkylation and secured the relative and absolute stereochemistry of the major isomers through single crystal analysis, we then sought to demonstrate the utility of the product esters. We recognized the synthetic potential the Pfp ester as a handle to prepare synthetically valuable 1,2-amino alcohols[21] as we have previously described that α-branched Pfp esters react instantaneously with gaseous ammonia to give the corresponding primary amides, which then undergo efficient stereoretentive rearrangement upon treatment with an appropriate oxidant.[5b] As a preliminary validation of this, alkylation of six arylacetic acid Pfp esters with two phenoxyallenes followed by ammonolysis produced the α-aryl-β-aryloxy primary amides. Following separation, the amides were converted via Hofmann rearrangement to the corresponding diastereomerically and enantiomerically pure *N*-carbamoyl-1,2-amino alcohols (**38**–**42**) in good overall yield.

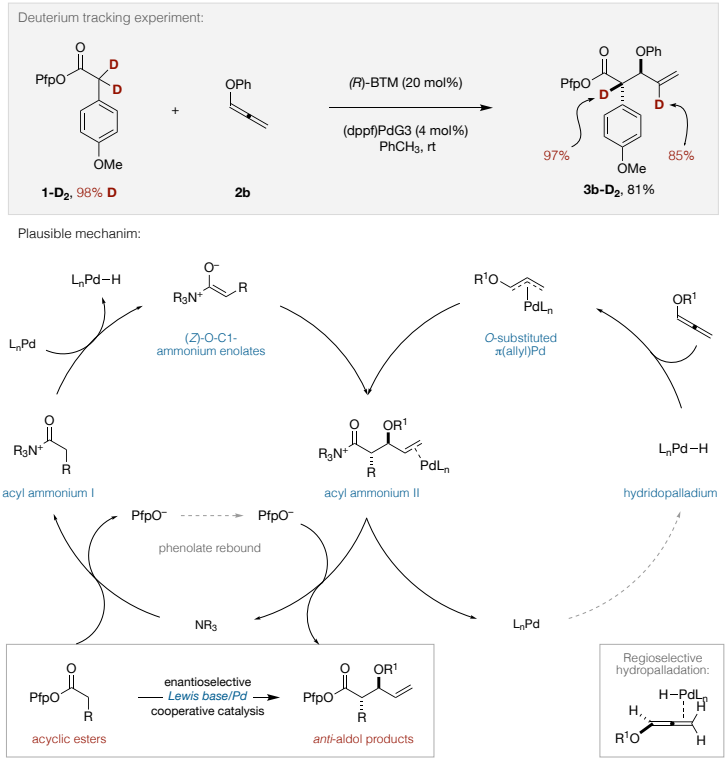


Scheme 3. Conversion to 1,2-amino alcohols.

From a mechanistic perspective two aspects of this reaction warrant closer scrutiny: (1) in contrast to established precedent,[5] no exogenous base is required to generate the ammonium enolate via enolization,[22] and (2) no exogenous Brønsted acid is required to generate the putative Pd–H intermediate necessary for oxyallene hydropalladation.[9] To gain insight into these two facets, we employed α,α-deuterium enriched **1**-D_2 in the alkylation with phenoxyallene **2b** (Scheme 4, top). We established that one of the deuterium atoms is incorporated *only* at the central carbon of the phenoxyallene (85%) while the other deuterium is fully retained (97%). The fidelity of this deuteron-transfer, and the fact that no product is formed in the absence of either catalyst, suggests that the requisite Pd–D is formed directly from an

acylammonium ion intermediate. This unveils a further cooperative aspect to this transformation where, in addition to playing a critical role in the key carbon–carbon bond forming event, the Pd catalyst is involved in the formation of both C1-ammonium enolate and RO-substituted π(allyl)Pd$^+$ species.

A plausible mechanism is presented in Scheme 4, bottom): reaction of the Pfp acyclic ester with the isothiourea catalyst (NR_3) liberates $PfpO^-$ and gives acylammonium ion I, which upon interception by Pd affords the corresponding (*Z*)-O-C1-ammonium enolate and Pd–H. Thereafter, regioselective hydropalladation of the terminal π-bond of the oxyallene by Pd–H results in *O*-substituted π(allyl)Pd,[23] which is intercepted by the ammonium enolate. Thereafter, decomplexation of Pd and turnover of the isothiourea via $PfpO^-$ rebound[5i,24,25] provides enantioenriched aldol products.



Scheme 4. Deuterium tracking and proposed mechanism.

In summary, we have developed an enantioselective alkylation of acyclic esters with oxyallenes that that is catalyzed by a cooperative isothiourea and palladium catalyst system. The reaction displays broad generality and provides direct access to useful *O*-substituted aldol products that would be challenging to access via alkylation/arylation of parent aldol scaffolds due to competing retro-aldol fragmentation. The further utility of the Pfp ester-containing products is also demonstrated via conversation to valuable 1,2-amino alcohols. Finally, brief initial mechanistic inquiry has revealed the manner of hydridopalladium formation and subsequent reaction with the oxyallene partners. This is our first success of leveraging the unique reactivity engendered by Pd–H species in concert with C1-ammonium enolate formation. In addition to greatly expanding the sphere of accessible reactivity, the efficiency of this two-catalyst construct processes raises the prospect of developing analogous stereodivegent reactions by judicious identification of chiral palladium catalysts compatible with this platform.[26]

Acknowledgements. We gratefully acknowledge the NIH (R01GM121573) and NSF (CHE1900229) for generous financial support. This project was partially supported by the IU Vice Provost for Research through the Research Equipment Fund.

References.

[1] a) J. R. Norton, J. Sowa Eds. Metal Hydrides Special Issue *Chem Rev.* **2016**, *116,* 8315–9000; b) V. V. Grushin, *Chem. Rev.* **1996**, *96*, 2011–2034.
[2] For selected recent and instructive examples, see: a) M.-S. Wu, Z.-Y. Han, L-Z. Gong, *Org. Lett.* **2021**, *23*, 636–641; b) Y.-L. Su, L.-L. Li, X.-L Zhou, Z.-Y. Dai, P.-S. Wang, L.-Z. Gong, *Org. Lett.* **2018**, *20*, 2403–2406; c) H. Wang, R. Zhang, Q. Zhang, W. Zi, *J. Am. Chem. Soc.* **2012**, *143*, 10948–10962; d) Q. Zhang, H. Yu, L. Shen, T. Tang, D. Dong, W. Chai, W. Zi, *J. Am. Chem. Soc.* **2019**, *141*, 14554–14559; e) F. A. Cruz, V. M. Dong, *J. Am. Chem. Soc.* **2017**, *139*, 1029–1032.
[3] S. Meyer, R. Gilmour,*Trends Chem.* **2020**, *2*, 959–961.
[4] For a review, see: G. J. Knox, L. Hutchings-Goetz, C. M. Pearson, T. N. Snaddon, *Topics in Current Chemistry* **2020**, *378*, 99–130.
[5] a) L. Hutchings-Goetz, C. Yang, J. W. B. Fyfe, T. N. Snaddon, *Angew. Chem. Int. Ed.* **2020**, *59*, 17556–17564; (b) C. M. Pearson, J. W. B. Fyfe, T. N. Snaddon, *Angew. Chem. Int. Ed.* **2019**, *58*, 10521–10527; (c) W. R. Scaggs, T. D. Scaggs, T. N. Snaddon, *Org. Biomol. Chem.* **2019**, *17*, 1787–1790; (d) L. Hutchings-Goetz, C. Yang, T. N. Snaddon, *ACS Catal.* **2018**, *8*, 10537–10544; (e) W. R. Scaggs, T. N. Snaddon, *Chem. Eur. J.* **2018**, *24*, 14378–14381; (f) K. J. Schwarz, C. Yang, J. W. B. Fyfe, T. N. Snaddon, *Angew. Chem. Int. Ed.* **2018**, *57*, 12102–12105; (g) K. J. Schwarz, C. M. Pearson, G. Cintro-Rosado, P. Liu, T. N. Snaddon, *Angew. Chem. Int. Ed.* **2018**, *57*, 7800–7803; (h) J. W. B. Fyfe, O. Kabia, C. M. Pearson, T. N. Snaddon, *Tetrahedron* **2018**, *74*, 5383–5391; (i) K. J. Schwarz, J. L. Amos, J. C. Klein, D. T. Do, T. N. Snaddon, *J. Am. Chem. Soc.* **2016**, *138*, 5214–5217.
[6] a) R. Mahrwald, ed. Modern Methods in Stereoselective Aldol Reactions. John Wiley & Sons, **2013**; b) R. Mahrwald, ed. Modern Aldol Reactions. John Wiley & Sons, **2004**
[7] J.-i. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109–9118.
[8] For a recent seminal report that deviates from this traditional ordinance in both aspects, see: T.-C. Wang, L.-F. Fan, Y. Shen, P.-S. Wang, L.-Z. Gong, *J. Am. Chem. Soc.* **2019**, *141*, 10616–10620.
[9] For authoritative reviews on the reactivity and synthetic value of alkoxyallenes, see: a) R. Zimmer, H.-U. Reissig, *Chem. Soc. Rev.* **2014**, *43*, 2888–2903; b) V. Schmiedel, H.-U. Reissig, *Curr. Org. chem.* **2019**, *23*, 2978–3005.
[10] a) B. M. Trost, C. Jäkel, B. Plietker, *J. Am. Chem.* **2003**, *125* 4438–4439; b) B. M. Trost, A. B. C. Simas, B. Plietker, C. Jäkel, J. Xie, *Chem. Eur J.* **2005**, *23* 7075–7082; c) B. M. Trost, J. Xie, J. D. Sieber, *J. Am. Chem. Soc.* **2011**, *133*, 20611–20622; d) M. Zhu, Q. Zhang, W. Zi, *Angew. Chem. Int. Ed.* **2021**, *60*, 6545–6552; e) H. Zhou, J.; Zhang, H. Yang, C. Xia, G. Jiang, *Angew. Chem. Int. Ed.* **2017**, *56*, 1077–1081.
[11] For discussion of isothioureas as enantioselective Lewis base catalysts, see: (e) J. Merad, J.-M. Pons, O. Chuzel, C. Bressy, *Eur. J. Org. Chem.* **2016**, 5589–5560.
[12] a) P. Liu, X. Yang, V. B. Birman, K. N. Houk, *Org. Lett.* **2012**, *14*, 3288–3291; b) V. D. Bumbu, V. B. Birman, *J. Am. Chem. Soc.* **2011**, *133*, 13902–13905; c) X. Yang, G. Lu, V. B. Birman, *Org. Lett.* **2010**, *12*, 892–895; (d) V. B. Birman, X. Li, *Org. Lett.* **2006**, *8*, 1351–1354.
[13] K. Jiang, T. Jia, M. Wang, J. Liao, P. Cao, *Org. Lett.* **2015**, *17*, 1070–1073.
[14] J. W. Raebiger, A. Miedaner, C. J. Curtis, S. M. Miller, O. P. Anderson, D. L. DuBois, *J. Am. Chem. Soc.* **2004**, *126*, 5502–5514.
[15] a) P. C. J. Kamer, P. W. N. van Leeuwen, , J. N. H. Reek, *Acc. Chem. Res.* **2001**, *34*, 895–904; b) P. W. N. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741–2770; c) P. Dierkes, P. W. N. van Leeuwen, *J. Chem. Soc., Dalton Trans.* **1999**, 1519–1530.
[16] The result was identical using the ligand enantiomer indicating that matched/mismatched effects were not operative.
[17] a) B. M. Trost, *Tetrahedron* **2015**, *71*, 5708–5733; b) B. M. Trost, M. R. Machacek, A. P. Aponick, *Acc. Chem. Res.* **2006**, *39*, 747–760.
[18] N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 916–920.
[19] For seminal and instructive investigations, see: a) P. R. Auburn, P. B. Mackenzie, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2033–2046; b) P. B. Mackenzie, J. Whelan, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2046–2054.
[20] CCDC deposition number: 2125386
[21] For pertinent reviews, see: a) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576; b) O. K. Karjalainen, A. M. P. Koskinen, *Org. Biomol. Chem.* **2012**, *10*, 4311–4326.
[22] For a rare 'base-free' example of C1-ammonium enolate formation, see: C. McLaughlin, A. M. C. Slawin, A. D. Smith, *Angew. Chem. Int. Ed.* **2019**, *58*, 15111–15119.
[23] I. Bernar, B. Fiser, D. Blanco-Ania, E. Gomez-Bengoa, F. J. T. Rutjes, *Org. Lett.* **2017**, *19*, 4211–4214

[24] S. S. Spoehrle, T. H. West, J. E. Taylor, A. M. Z. Slawin, A. D. Smith, *J. Am. Chem. Soc.* **2017**, *139*, 11895–11902
[25] W. C. Hartley, T. J. C. O'Riordan, A. D. Smith, *Synthesis*, **2017**, *49*, 3303–3310.
[26] For instructive reviews of stereodivergent organo/transition metal cooperative catalysis, see: a) S. M. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2017**, *139*, 5627–5639; b) I. Beletskya, C. Najera, M. Yus, *Chem. Rev.* **2018**, *118*, 5080.