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A Regio- and Stereodivergent Synthesis of Homoallylic Amines via a One-Pot Cooperative Catalysis-based Allylic Alkylation/Hofmann Rearrangement Strategy

Colin M. Pearson,[+] James W. B. Fyfe[+] and Thomas N. Snaddon*[a]

Dedicated to Professor Alois Fürstner

Abstract: Herein, we report a modular synthetic route to linear and branched homoallylic amines that operates *via* a sequential one-pot Lewis base/transition metal catalyzed allylic alkylation/Hofmann rearrangement strategy. This protocol is operationally trivial, proceeds from simple and easily prepared substrates and catalysts, and enables all aspects of regio- and stereoselectivity to be controlled via a conserved experimental protocol. Overall, the high levels of enantio-, regio- and diastereoselectivity obtained, in concert with the ability to access orthogonally-protected or free amines, render this a straightforward and effective approach for the preparation of useful enantioenriched homoallylic amines. We have also demonstrated the utility of the products in the context pharmaceutical synthesis.

Introduction

Enantiomerically-enriched carbinamines are among the most prevalent structural motifs in bioactive alkaloids and pharmaceuticals (Figure 1a).[1] They also constitute a diversity of essential chemical building blocks for applications in asymmetric synthesis and catalysis, and methods for their synthesis have been intensely pursued. Homoallylic amines, in particular, are widely employed for the synthesis of unnatural amino acids and bespoke heterocycles via elaboration of the embedded amine and alkene functional groups.[2] Therefore, the development of operationally straightforward, direct and modular synthetic routes to homoallylic amines, which are capable of incorporating a diversity of functionality whilst simultaneously controlling reaction regio- and stereoselectivity, is of continuing importance.

The catalytic asymmetric synthesis of homoallylic amines continues to be the subject of considerable effort. The catalyzed addition of allylmetal nucleophiles to imine (and related) electrophiles has attracted significant attention (Figure 1b, left).[3] Transition metal and Brønsted acid catalyzed addition of allylboron nucleophiles is especially effective and provides branched products with high levels of enantio- and diastereoselectivity.[4] More recently, allylcopper nucleophiles

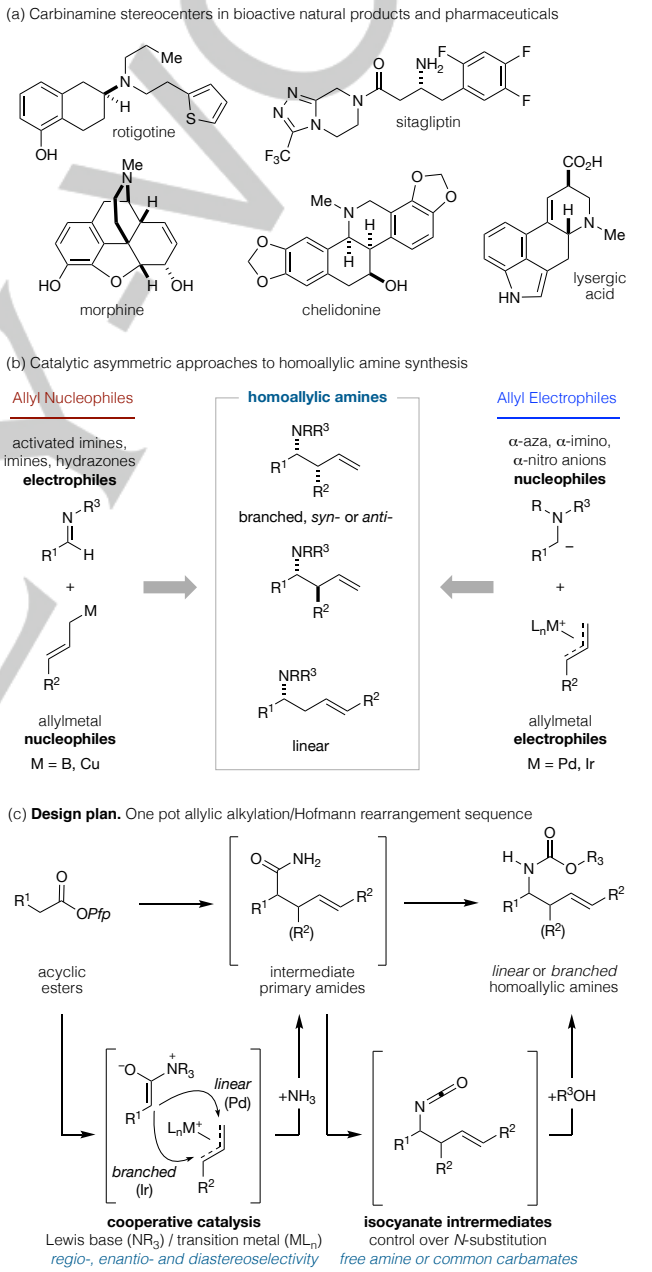

Figure 1. a) Examples of secondary amine-containing bioactive molecules. b) Complementary polarity approaches to catalytic asymmetric homoallylic amine synthesis. c) This work: A modular, one pot synthesis of homoallylic amines featuring a cooperative Lewis base/transition metal catalysed regio- and stereodivergent allylic alkylation/Hofmann rearrangement strategy.

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that can be conveniently prepared *in* situ, undergo enantioselective reaction with aldimines and ketimines under the action of both metal and non-metal catalysts.[4i-k] The complementary polarity approach using π(allyl)metal electrophiles (Figure 1b, right) has also been explored. Nitro-stabilized anions,[5-7] glycine-derived metalloenolates[8-10] and fluorenyl imine-derived anions[11] have been most intensively studied and are effective nucleophiles for a host of enantioselective Pd- and Ir-catalyzed allylic alkylation reactions. While each of these methods is effective and efficient they cannot be easily modified to rationally prepare *linear* or *branched* homoallylic amines. Thus, a general and flexible protocol for their preparation remains a significant challenge.

As part of a long-standing program directed toward catalyzed and stereocontrolled carbon–carbon bond formation, we sought to provide a straightforward, operationally trivial and modular catalysis-based protocol for the regio- and stereodivergent[12] synthesis of enantioenriched homoallylic amines.[13] Principal among our concerns was catalyst control over all aspects of selectivity during carbon–carbon bond formation, whilst also working within a useful *N*-protecting group regime. Herein, we describe such a protocol, which provides a straightforward and modular preparation of these valuable building blocks.

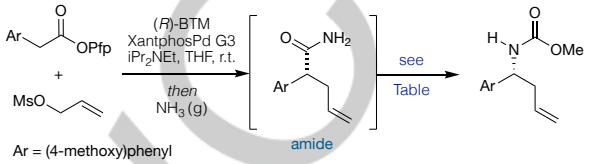
Reaction Design. We have invested considerable effort in the development of Lewis base/transition metal cooperative catalysis to control enantioselective C(sp^3)–C(sp^3) bond formation between acyclic pentafluorophenyl esters (Pfp esters, hereafter) and allyl electrophiles.[14,15] This versatile platform proceeds via the union of C1-ammonium enolate nucleophiles[16,17] and π(allyl)Pd electrophiles[18] and provides highly enantioenriched and functionalized α-branched esters that can be readily diversified without compromising optical purity.[19] Two crucial features of this orthogonal regime are relevant to our proposed synthesis of homoallylic amines (Figure 1c). Firstly, all aspects of enantio-, regio- and diastereodivergent C(sp^3)–C(sp^3) formation could be controlled by judicious choice of the Lewis base/transition metal catalyst combination (see Figure 1c, cooperative catalysis). Secondly, rapid in situ conversion of product Pfp esters (not shown) to intermediate primary amides[14b,20] would permit subsequent stereospecific Hofmann-type rearrangement[21,22] to forge the necessary C(sp^3)–N bond via isocyanates (see Figure 1c, isocyanate intermediates). These could be intercepted with an appropriate alcohol (R^1-OH) to give the corresponding carbamate-protected or unprotected enantioenriched linear or branched homoallylic amines. We also expected that the projected efficiency of each constituent transformation in the sequence would provide ample opportunity for a sequential single pot process.

Here, we report the successful realization of this design, which provides a modular, operationally-trivial and convenient one-pot enantioselective protocol for the regio- and stereodivergent preparation homoallylic amines.[23]

Results and Discussion

Oxidant Assessment and Optimization of a One-pot Protocol. Our initial efforts focused on identifying an appropriate oxidant to induce stereospecific Hofmann-type C→N rearrangement of enantioenriched amides.[24,25] In the presence of methanol a variety of oxidants effectively mediated the Hofmann rearrangement of (*R*)-2-(4-methoxyphenyl)pent-4-enamide **A** giving the corresponding methyl carbamate-protected homoallylic amine (Table 1).[25a] We initially identified [bis(trifluoroacetoxy)iodo]benzene (PIFA, 1.5 equivalents) in combination with potassium hydroxide (2.5 equivalents) in methanol as an effective system, which gave the rearranged product in 90% isolated yield and with complete stereotransfer (96:4 er, Entry 1). Further optimization (Entries 6–9) resulted in a mixed solvent system of THF/MeOH in 2:1 ratio at 60 °C from which desired homoallylic methyl carbamate was isolated in quantitative yield (Entry 9. For full solvent screening, see Supporting Information). These conditions obviated the need for potassium hydroxide, which not only simplified the protocol

Table 1. Optimization of oxidative Hofmann rearrangement and application to full one-pot allylation–Hofmann rearrangement sequence.



Entry[a]	Oxidant	Base	Solvent	Temp. [°C]	Yield [%][b]
1	PIFA	KOH	MeOH	rt	90
2	PIDA	KOH	MeOH	rt	80
3	PhI/oxone	-	MeOH	rt	-
4	$Pb(OAc)_4$	-	MeOH	rt	89
5	NBS	DBU	MeOH	rt	76
6	PIFA	KOH	THF/MeOH (25:1)	rt	43
7	PIFA	KOH	THF/MeOH (2:1)	rt	66
8	PIFA	-	THF/MeOH (2:1)	rt	80
9	PIFA	-	THF/MeOH (2:1)	60	99
10[c]	PIFA	-	THF/MeOH (2:1)	60	67
11[c,d]	PIFA	-	THF/MeOH (2:1)	60	74 (73)

[a] Reactions run on 0.1 mmol scale from isolated amide. [b] ^{1}H NMR yield calculated using internal standard. [c] Full one-pot procedure from starting Pfp ester (0.1 mmol scale). [d] 2.0 equivalents of PIFA were used.

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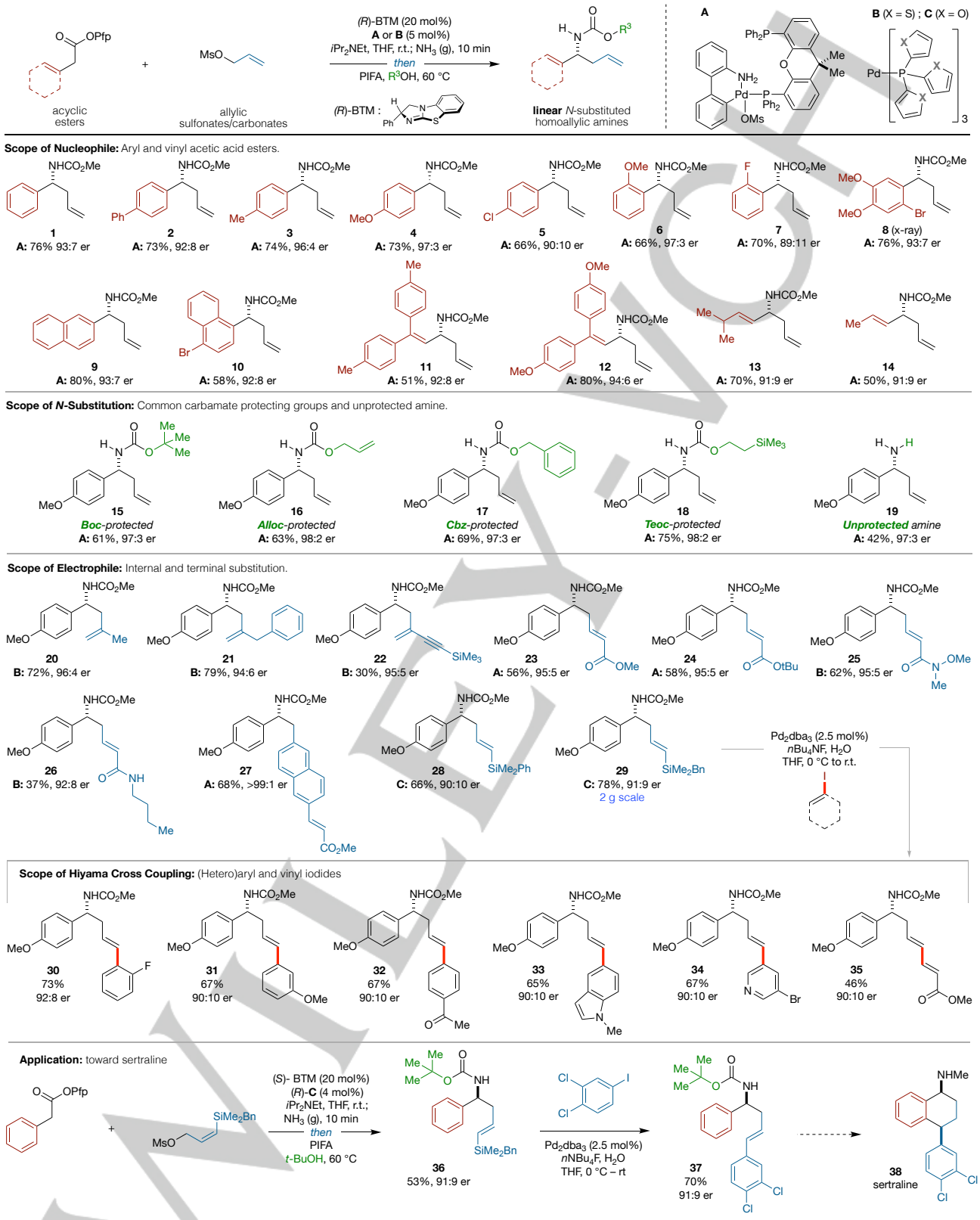

Scheme 1. Preparation of enantioenriched linear homoallylic amines: evaluation of nucleophile scope, *N*-substitution (*via* preparation of common carbamate-protected amines and free amine) and electrophile scope. A combination of these components in the synthesis of **37**, a key intermediate *en route* to the synthesis of sertraline **38**.

considerably but also raised the prospect of greater functional group tolerance. These conditions were then applied to a streamlined cooperative catalysis–rearrangement protocol. Employing Birman's benzotetramisole (BTM)[26] in combination with Buchwald's Xantphos-ligated 3rd generation Pd precatalyst (XantphosPd G3),[27] allylation via enantioselective cooperative catalysis was followed by instantaneous formation of the corresponding primary amide by bubbling NH_3 gas through the reaction mixture. Thereafter, treatment of the reaction mixture with PIFA and MeOH gave the methyl carbamate-protected homoallylic amine in 67% yield (Entry 10). Increasing the stoichiometry of PIFA to 2 equivalents gave the carbamate in an enhanced 73% isolated yield and with excellent enantioenrichment (97:3 er, Entry 11).

Linear Homoallylic Amine Synthesis with Palladium. With these optimized conditions in hand we examined the scope of nucleophile (Scheme 1). A range of aryl and alkenyl acetic acid esters successfully afforded the corresponding carbamate-protected homoallylic amines in good isolated yields and with high levels of enantioenrichment. Noteworthy is the tolerance of aryl halides (**5**, **7**–**8**, **10**) electron-rich arenes (**2**–**4**, **6**) and π-extended arenes (**9**, **10)** to this oxidative protocol. Finally, both conjugated and non-conjugated alkene-substituted esters (**11**–**14**) were effective; significant is the preparation of **14**, which is chiral only by virtue of the alkene position. As yet, we have been unsuccessful in our attempts to engage either aliphatic esters or terminal alkyl-substituted electrophiles in this chemistry; both are the subject of ongoing study.

We then evaluated the scope of *N*-substitution (Scheme 1). In many approaches to homoallylic amine synthesis nitrogen substitution needs to be tailored to enhance reactivity and/or provide a site for catalyst engagement. Here, simply changing the identity of the alcohol used to trap the putative isocyanates derived from oxidative Hofmann-type rearrangement provides access to the most commonly encountered and synthetically orthogonal carbamate protective groups;[28] *tert*-Butoxycarbonyl- (Boc, **15**), allyloxycarbonyl- (Alloc, **16**), benzyloxycarbonyl- (Cbz, **17**) and 2-(trimethylsilyl)-ethoxycarbonyl- (Teoc, **18**) protected amines are all obtained with high levels of enantioselectivity. Furthermore, employing water as the nucleophile provides the corresponding free amine **19** with similar enantioenrichment. Here, the lower isolated yield (42%) is due to more difficult chromatographic purification rather that compromised protocol efficiency, as evidenced by spectroscopic analysis of the crude material. Thereafter, we move to examine the scope of allyl sulfonate electrophiles (Scheme 1). Employing $Pd[P(2\text{-thienyl})_3]_3$ (**B**) as the catalyst[29] enabled 2-substituted allyl electrophiles to react effectively giving functionalized homoallylic amines **20**–**22**,[14b] the latter containing a trimethylsilylacetylene substituent. Using the same catalyst ester (**23**,**24**), Weinreb amide (**25**) and secondary amide (**26**) -substituted allyl electrophiles were also effective.[14f] Recourse to $P(2\text{-furyl})_3$ (**C**) as a supporting ligand enabled the synthesis of silyl-substituted products **28** and **29**.[14c] Functionalized electrophiles **23**–**29** are particularly noteworthy as their incorporation via allylmetal addition to imines would, beyond challenges associated with enantio- and regioselectivity, be precluded due to functional group compatibility issues and concerns over α– vs γ– nucleophile addition.[30] Finally, the preparation of an α,β-unsaturated ester-substituted homobenzylic amine **27** was possible using a 2-naphthylic phenylphosphate electrophile in combination with XantphosPd G3.[14d] Again, preparation of **27** via common imine addition reactions would be problematic. The major limitation of this protocol concerns the poor compatibility of the styrenyl motif within the electrophile scaffold, which leads to numerous unidentifiable products during the oxidative rearrangement. To address this limitation, benzyldimethylsilyl-substituted carbamate **29** could be directly elaborated in diverse fashion via Pd-catalyzed Hiyama cross coupling[31,32] with a range of (hetero)aryl- and alkenyl iodides without erosion of enantioenrichment (Scheme 2, **30**–**35**); ketone (**32**), indole (**33**), pyridine (**34**) and dienoate (**35**) -containing products are all accessible from a common intermediate (**29**). We expect that late-stage diversification in this manner will prove convenient for the preparation of varied homoallylic amine structures of interest to therapeutic development. Finally, to demonstrate the utility of this method to pharmaceutically-relevant molecules we prepared Boc-protected homoallylic amine **36** using the protocol described and elaborated this via Hiyama cross-coupling to **37**, which has been converted to selective serotonin reuptake inhibitor sertraline **38** (Scheme 1).[11a,33]

Branched Homoallylic Amine Synthesis with Iridium. Having established a general and modular protocol for the synthesis of carbamate-protected *linear* homoallylic amines we sought to address the of *branched* regioisomers with control over diastereoselectivity (Scheme 2). We expected this protocol would translate to the corresponding branched-selective cooperative BTM/Iridium-catalyzed process, where control over both stereogenic centers should proceed under the independent direction of Lewis base and Ir catalysts, respectively, and provide stereodivergent access to any stereoisomer.[15b] Employing Hartwig's cyclometalated iridium(I)-phosphoramidite (*S*)-**D** [(*S*)-Ir] in combination with (*R*)-BTM within the same experimental protocol gave (1*R*,2*S*)-**39** in 83% yield, 95:5 dr and as a single enantiomer (for detailed optimization see the Supporting Information). As previously described,[15b] judicious choice of catalyst permutations during allylic alkylation provides stereodivergent access to all possible stereoisomers of **39** with similar efficiency. Thus, this protocol constitutes a formal catalytic stereodivergent cinnamylation of imines and represents a completely catalyst-controlled evolution of Leighton's branched selective reagent-controlled synthesis of homoallylic amines.[34] As the stereodivergent nature of the allylic alkylation has previously been confirmed[15b] we assessed the branched-selective synthesis of homoallylic amine via *unbiased* nucleophile, electrophile and catalyst combinations. As expected, in this protocol both aryl and alkenyl nucleophiles were effective in combination with a range of electrophilic partners (**40**-**50**). Furthermore, halides, nitroarene, indole, thiophene, pyridine, and pinacol borane esters are all tolerated. More specifically, electron-rich aryl (*anti*-**40**, *syn*-**41**), indole (*syn*-**42**) and thiophene (*anti*-**43**)-substituted electrophiles all provided products with high levels of diastereo- and enantioselectivity, thus demonstrating excellent individual catalyst control. Interrogation of electron-deficient F-, NO_2-, and Cl-substituted aryl electrophiles (*syn*-**44**, *anti*-**45**, *syn*-**46**) revealed an unexpected influence on

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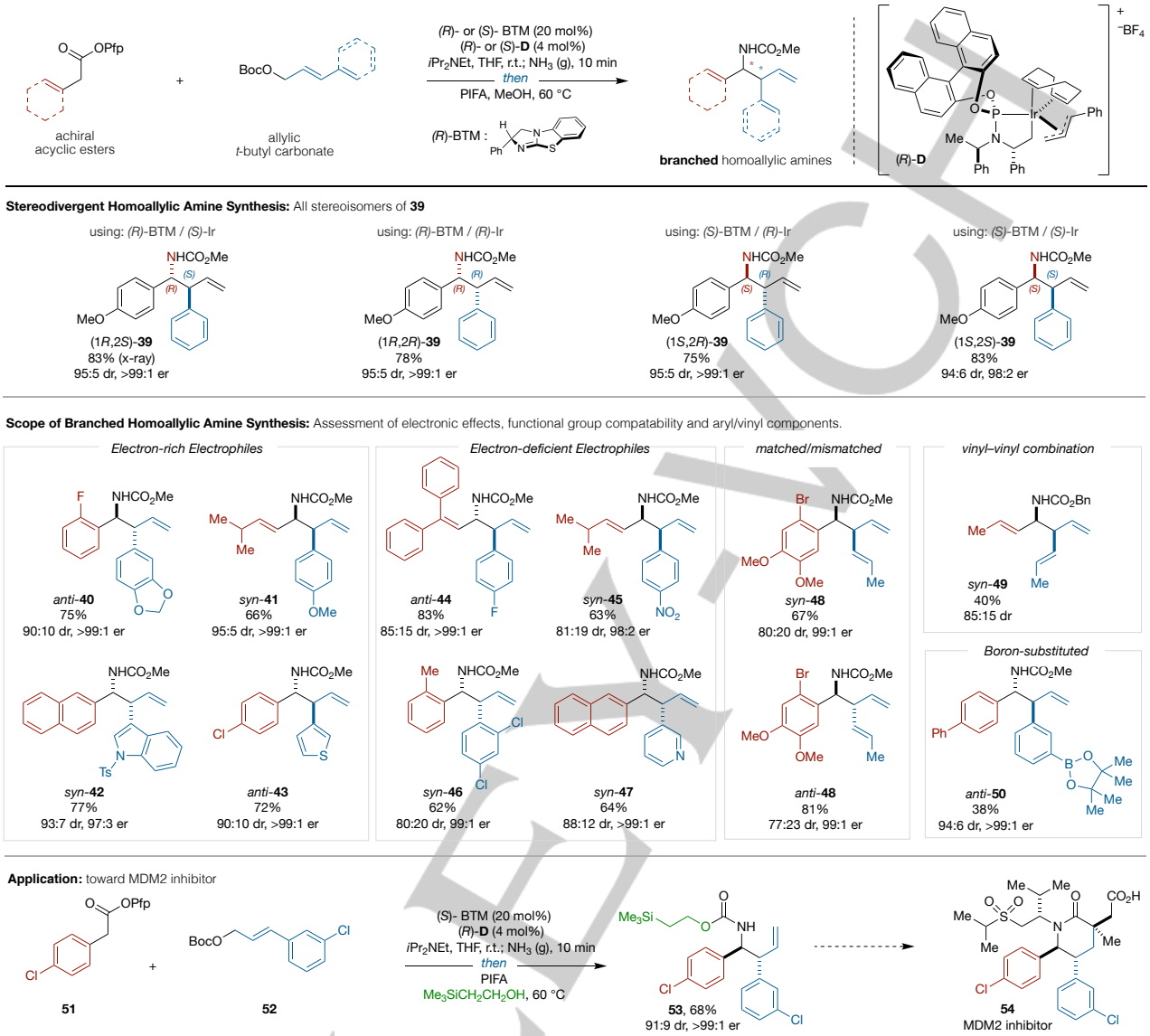

Scheme 2. Preparation of enantioenriched branched homoallylic amines: The fully stereodivergent preparation of branched homoallylic amines **39** via different catalyst enantiomer combinations. The unbaised evaluation of scope via nucleophile/electrophile combinations and application to the synthesis of MDM2-inhibitor core scaffold **53**.

diastereoselectivity (ca 80:20). In each case the major diastereoisomer was produced in high enantiopurity. This was also true when employing an electron-deficient pyridyl-substituted heteroaromatic electrophile (*syn*-**47**). Similarly, alkene-substituted electrophiles also exhibited more modest diastereoselectivity, which does not arise due to matched–mismatched interaction between catalysts (see *syn*-**48** vs. *anti*-**48**). Again, the exceptional enantioselectivity of the major diastereoisomer is unaffected. Preparation of *syn*-**49** demonstrated the tolerance of vinyl substituents on both reaction components. Boronic ester substituted electrophiles (*anti*-**50**) were also tolerated and provide another synthetic handle for further functionalization. Finally, this procedure was used to construct the core scaffold **53** of the MDM2 inhibitor **54**[35] with excellent control over both diastereo- and enantioselectivity. Overall, when integrated with BTM/Ir-catalyzed allylic alkylation, this one-pot protocol provides robust stereocontrolled access to branched homoallyl amines with incorporation of diverse functionality.[36]

Conclusion

By pairing cooperative Lewis base/transition metal catalysis with stereospecific C–N bond formation we have developed a unified and operationally simple experimental protocol for the catalytic enantioselective synthesis of homoallylic amines. This protocol exhibits broad functional group tolerance, and enantio-, regio- and

diastereoselectivity are addressed by judicious choice of the appropriate Lewis base/transition metal catalyst combination. Finally, in situ stereospecific C–N rearrangement enables nitrogen substitution to be augmented within the confines of a useful protecting group regime. Limitations to this protocol include the sensitivity of styrenyl motifs to the oxidation step; however, this can be circumvented by elaboration of a vinylsilane motif via Hiyama cross coupling. Finally, neither aliphatic esters nor terminal alkyl-substituted electrophiles are productive partners in this process; both aspects are the subject of current study within our laboratory. Nonetheless, we expect this operationally straightforward and modular protocol will prove useful to those researchers requiring access to enantioenriched homoallylic amines. The starting Pfp ester are inexpensive to prepare in a single step from the precursor acid and are of established utility as acyl donors for peptide coupling.[20] Similarly, the electrophiles used can be readily accessed using robust methods. Overall, this study demonstrates the potential of combining simultaneous catalysis events with subsequent value-added transformations in stereoselective chemical synthesis.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: amine • ammonium enolate • alkylation • palladium • rearrangement

[1] *Amines: Synthesis, Properties and Applications*; S. A. Lawrence, Cambridge University Press, Cambridge, **2004**.

[2] B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2010**, *39*, 1656–1691.

[3] For reviews, see: (a) M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2013**, *113*, 5595–5698; (b) M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774–7854; (c) S. Kobayashi, Y. Mori, J. S. Fossey, M. M. Salter, *Chem. Rev.* **2011**, *111*, 2626–2704.

[4] For reviews, see: (a) C. Diner, K. J. Szabo, *J. Am. Chem. Soc.* **2017**, *139*, 2–14; (b) T. R. Ramadhar, R. A Batey, *Synthesis* **2011**, 1321–1346; (c) H.-X. Huo, J. R. Duvall, M.-Y. Huang, R. Hong, *Org. Chem. Front.* **2014**, *1*, 303–320. For selected examples, see: (d) M. Fujita, T. Nagano, U. Schneider, T. Hamada, C. Ogawa, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 2914–2915; (e) S. J. Jonker, C. Diner, G. Schulz, H. Iwamoto, L. Eriksson, K. Szabó, *Chem. Commun.* **2018**, *54*, 12852–12855; (f) R. J. Morrison, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2018**, *57*, 11654–11661; (g) H. Jang, F. Romiti, S. Torker, A. H. Hoveyda, *Nat. Chem.* **2017**, *9*, 1269–1275; (h) F. W. van der Mei, H. Miyamoto, D. L. Silverio, D. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 4701–4706; (i) Silverio, S. Torker, T. Pilyugina, E. M. Vieira, M. L. Snapper, F. Haeffner, A. H. Hoveyda, *Nature* **2013**, *494*, 216–221; (j) E. M. Vieira, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 3332–3335; (k) S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2007**, *129*, 15398–15404; (l) K. Yeung, R. E. Ruscoe, J. Rae, A. P. Pulis, D. J. Procter, *Angew. Chem. Int. Ed*. **2016**, *55*, 11912–11916; (m) B. Alam, C. Diner, S. Jonker, L. Eriksson, K. J. Szabo, *Angew. Chem. Int. Ed.* **2016**, *55*, 14417–14421; (n) P. Zhang, I. A. Roundtree, J. P. Morken, *Org. Lett.* **2012**, *14*, 1416–1419; (o) G. Dutheuil, N. Selander, K. J. Szabo, V. K. Aggarwal, *Synthesis* **2008**, *14*, 2293–2297; (p) M. Murata, S. Watanabe, Y. Masuda *Tetrahedron Lett.* **2000**, *41*, 5877–5880; (q) T. Ishiyama, T.-A. Ahiko, N. Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889–6892.

[5] (a) B. M. Trost, J.-P. Surivet, *Angew. Chem. Int. Ed.* **2000**, *39*, 3122–3124; (b) B. M. Trost, J.-P. Surivet, *J. Am. Chem. Soc.* **2000**, *122*, 6291–6292.

[6] K. Ohmatsu, M. Ito, T. Kunieda, T. Ooi, *Nat. Chem.* **2012**, *4*, 473–477.

[7] X.-F. Yang, W.-H. Yu, C.-H. Ding, Q.-P. Ding, S.-L. Wan, X.-L. Hou, L.-X. Dai, P.-J. Wang, *J. Org. Chem.* **2013**, *78*, 6503–6509.

[8] M. Nakoji, T. Kanayama, T. Okino, Y. Takemoto, *J. Org. Chem.* **2002**, *67*, 7418–7423.

[9] T. Kanayama, K. Yoshida, H. Miyabe, Y. Takemoto, *Angew. Chem. Int. Ed.* **2003**, *42*, 2054–2056.

[10] (a) X. Huo, J. Zhang, J. Fu, R. He, W. Zhang, *J. Am. Chem. Soc.* **2018**, *134*, 2080−2084; (b) X. Huo, R. He, J. Fu, J. Zhang, G. Yang, W. Zhang, *J. Am. Chem. Soc.* **2016**, *139*, 9819–9822.

[11] (a) J. Liu, C.-G. Cao, H.-B. Sun, X. Zhang, D. Niu, *J. Am. Chem. Soc.* **2016**, *138*, 13103−13106; (b) L. Wan, L. Tian, J. Liu, D. Niu, *Synlett* **2017**, *28*, 2051–2056.

[12] For a recent review of catalyst-controlled stereodivergence, see: (a) S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2017**, *139*, 5627–5639. For selected additional examples, see: (b) F. A. Cruz, V. M. Dong, *J. Am. Chem. Soc.* **2017**, 139, 1029–1032; (c) S. Kassem, A. T. Lee, D. A. Leigh, V. Marcos, L. I. Palmer, S. Pisano, *Nature* **2017**, *549*, 374–378; (d) T. Sandmeier, S. Krautwald, H. F. Zipfel, E. M. Carreira, *Angew. Chem Int. Ed.* **2015**, *54*, 14363–14367; (e) S. Krautwald, M. A. Schafroth, D. Sarlah, E. M. Carreira, *J. Am. Chem. Soc.* **2014**, *136*, 3020–3023; (f) S. Krautwald, D. Sarlah, M. A. Schafroth, E. M. Carreira, *Science* **2013**, *340*, 1065–1068.

[13] For an excellent modular stereodivergent approach to enantioenriched *allylic* amines bearing vicinal stereogenic centers via three sequential catalyst-controlled reactions, see:(a) P. Tosatti, A. J. Campbell, D. House, A. Nelson, S. P. Marsden *J. Org. Chem.* **2011**, *76*, 5495.–5510

[14] (a) K. J. Schwarz, J. L. Amos, J. C. Klein, D. T. Do, T. N. Snaddon, *J. Am. Chem. Soc.* **2016**, *138*, 5214–5217; (b) K. J. Schwarz, C. M. Pearson, G. A. Cintron-Rosado, P. Liu, T.N. Snaddon, *Angew. Chem Int. Ed.* **2018**, *57*, 7800–7803; (c) J. W. B. Fyfe, O. M. Kabia, C. M. Pearson, T. N. Snaddon, *Tetrahedron* **2018**, *74*, 5383–5391; (d) K. J. Schwarz, C. Yang, J. W. B. Fyfe, T. N. Snaddon, *Angew. Chem. Int. Ed.* **2018**, *57*, 12102–12105; (e) W. R. Scaggs, T. N. Snaddon, *Chem. Eur. J.* **2018**, *24*, 14378–14381; (f) L. Hutchings-Goetz, C. Yang, T. N. Snaddon, *ACS Catal.* **2018**, *8*, 10537−10544; (g) W. R. Scaggs, T. D. Scaggs, T. N. Snaddon, *Org. Biomol. Chem.* **2019**, *17*, 1787–1790.

[15] For other examples of C1-ammonium enolates being employed in conjunction with transition metal catalysis, see: (a) S. S. Spoehrle, T. H. West, J. E. Taylor, A. M. Z. Slawin, A. D. Smith, *J. Am. Chem. Soc.* **2017**, *139*, 11895–11902; (b) Z. Jiang, J. J. Beiger, J. F. Hartwig, *J. Am. Chem. Soc.* **2017**, *139*, 87–90; (c) X. Lu, L. Ge, C. Cheng, J. Chen, W. Cao, X. Wu, *Chem. Eur. J.* **2017**, *23*, 7689–7693; (d) J. Song, Z.-J. Zhang, L.-Z.; Gong, *Angew. Chem. Int. Ed.* **2017**, *56*, 5212–5216; (e) J. Song, Z.-J. Zhang, S.-S. Chen, T. Fan, L.-Z. Gong, *J. Am. Chem. Soc.* **2018**, 140, 3177–3180.

[16] For reviews of C1-ammonium enolate generation and reactivity, see: (a) W. C. Hartley, T. J. C. O'Riordan, A. D. Smith, *Synthesis* **2017**, *49*, 3303–3310; (b) L. C. Morrill, A. D. Smith, *Chem. Soc. Rev.* **2014**, *43*, 6214–6226; (c) M. J. Gaunt, C. C. Johansson, *Chem. Rev.* **2007**, *107*, 5596–5605; (d) D. H. Paull, A. Weatherwax, T. Lectka, *Tetrahedron* **2009**, *65*, 6771–6803; (e) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985–3012.

[17] For computation supporting the structure of benzotetramisole-derived C1-ammonium enolates, including a discussion of stereocontrol, see: (a) T. H. West, D. M. Walden, J. E. Taylor, A. C. Brueckner, R. C. Johnstone, P. H.-Y. Cheong, G. C. Lloyd-Jones, A. D. Smith, *J. Am. Chem. Soc.* **2017**, *139*, 4366–4375; (b) E. R. T. Robinson, D. M. Waldon, C. Fallan, M. D. Greenhalgh, P. H.-Y. Cheong, A. D. Smith, *Chem. Sci.* **2016**, *7*, 6919–6927.

[18] For reviews concerning catalyzed enantioselective reactions proceeding via π(allyl)Pd electrophiles, see: (a) J. Tsuji, *Tetrahedron* **2015**, *71*, 6330–6348; (b) B. M. Trost *Tetrahedron* **2015**, *71*, 5708–5733; (c) J. D. Weaver, A. Recio, III, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846–1913; (d) B. M. Trost, M. R. Machacek, A. P. Aponick, *Acc. Chem. Res.* **2006**, *39*, 747–760; (e) B. M. Trost, M. L. Crawley,. *Chem. Rev.* **2003**, *103*, 2921–2944; (f) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422.

[19] For computation concerning benzotetramisole-containing C1-ammonium enolates reacting with cationic π(allyl)Pd(II) electrophiles via an outer-sphere mechanism, see: Ref 14b.

[20] Pentafluorophenyl esters are established acyl donors in peptide bond formation. For examples, see: (a) L. M. Gayo, M. J. Suto, *Tetrahedron Lett.* **1996**, *37*, 4915–4918; (b) M. Green, J. Berman, *Tetrahedron Lett.* **1990**, *31*, 5851–5852; (c) E. Atherton, L. R. Cameron, R. C. Sheppard, *Tetrahedron* **1988**, *44*, 843–857; (d) L. Kisfaludy, J. Roberts, R. Johnson, G. L. Mayers, J. Kovacs, *J. Org. Chem.* **1970**, *35*, 3563–3565.

10.1002/anie.201905426

[21] *Strategic Applications of Named Reactions in Organic Synthesis*; L. Kurti, B. Czakó, Elsevier Academic Press, Amsterdam, **2005**.

[22] There are isolated reports of the Hofmann rearrangement being used to prepare homoallylic amines; however, none of these constitute a general method for the regio- and stereodivergent synthesis of enantioenriched homoallylic amines, see: (a) K. G. M. Kou, S, Kulyk, C. J. Marth, J. C. Lee, N. A. Doering, B. X. Li, G. M. Galego, T. P. Lebold, R. Sarpong, *J. Am. Chem. Soc.* **2017**, *139*, 13882–13896; (b) C. J. Marth, G. M. Galego, J. C. Lee, T. P. Lebold, S. Kulyk, K. G. M. Kou, J. Qin, R. Lilien, R. Sarpong, *Nature* **2015**, *528*, 493–498; (c) M. Ito, Y. Kondon, H. Nambu, M. Anada, K. Takeda, S. Hashimoto, *Tetrahedron Lett.* **2015**, *56*, 1397–1400; (d) S. Umezaki, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2013**, *15*, 4230–4233; (e) C. Sosale, M. V. Rao, *Beilstein J. Org. Chem.* **2012**, *8*, 1393–1399; (f) J.-H. Ye, Y. Huang, R.-Y. Chen, *Org. Prep. Proc. Int.* **2003**, *35*, 429–432; (g) K. A. Newlander, J. F. Callahan, M. L. Moore, T. A. Tomaszek Jr., W. F. Huffmann, *J. Med. Chem.* **1993**, *36*, 2321–2331.

[23] For an excellent recent example of stereodivergence via the addition of stereodefined (*E)* or *(Z)* allylboronic acid nucleophiles to indoles and dihydroisoquinolines, see Ref 4m.

[24] For a recent review, see: A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328–3435.

[25] (a) A. A. Zagulyaeva, C. T. Banek, M. S. Yusubov, V. V. Zhdankin, *Org. Lett.* **2010**, *12*, 4644–4647; (b) P. Liu, Z. Wang, X. Hu, *Eur. J. Org. Chem.* **2012**, 1994–2000; (c) A. Yoshimura, K. R. Middleton, M. W. Luedtke, C. Zhu, V. V. Zhdankin, *J. Org. Chem.* **2012**, *77*, 11399–11404; (d) A. Yoshimura, M. W. Luedtke, V. V. Zhdankin, *J. Org. Chem.* **2012**, *77*, 2087–2091.

[26] (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. 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.

[27] N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2012**, *4*, 916–920.

[28] *Protecting Groups*; P .J. Kocienski, 3rd Edition, Thieme, Stuttgart, **2005**.

[29] W. Li, Y. Han, B. Li, C. Liu, Z. Bo, *J. Polym. Sci. A* **2008**, *46*, 4556–4563.

[30] (a) For access to related products via vinylogous Mannich reactions, see: M. Sickert, C. Schneider, *Angew. Chem. Int. Ed.* **2008**, *47*, 3631–3634.

[31] For reviews of Pd-catalyzed cross coupling of organosilicon compounds, see: (a) Y. Nakao, T. Hiyama, *Chem. Soc. Rev.* **2011**, *40*, 4893–4901; (b) S. E. Denmark, J. Liu, *Angew. Chem. Int. Ed.* **2010**, *49*, 2978–2986; (c) H. F. Sore, W. R. Galloway, D. R. Spring, *Chem. Soc. Rev*. **2011**, *41*, 1845–1866.

[32] (a) B. M. Trost, M. R. Machacek, Z. T. Ball, *Org. Lett.* **2003**, *5*, 1895–1898; (b) M. G. McLaughlin, C. A. McAdam, M. J. Cook, *Org. Lett.* **2015**, *17*, 10–13.

[33] R. Kalshetti, V. Venkataramasubramanian, S. Kamble, A. Sudalai, *Tetrahedron Lett.* **2016**, *57*, 1053–1055.

[34] (a) J. D. Huber, J. L. Leighton, *J. Am. Chem. Soc.* **2007**, *129*, 14552–14553; (b) J. D. Huber, N. R. Perl, J. L. Leighton, *Angew. Chem. Int. Ed.* **2008**, *47*, 3037–3039.

[35] D. Sun, Z. Li, Y. Rew, M. Gribble, M. D. Bartberger, H. P. Beck, J. Canon, A. Chen. X. Chen, D. Chow, J. Deignan, J. Duquette, J. Eksterowicz, B. Fisher, B. M. Fox, J. Fu, A. Z. Gonzalez, F. Gonzalex-Lopez De Turiso, J. B. Houze, X. Huang, M. Jiang, L. Jin, F. Kayser, J. Liu, M.-C. Lo, A. M. Long, B. Lucas, L. R. McGee, J. McIntosh, J. Mihalic, J. D. Oliner, T. Osgood, M. L. Peterson, P. Roveto, A. Y. Saiki, P. Shaffer, M. Toteva, Y. Wang, Y. C. Wang, S. Wortman, P. Yakowec, X. Yan, Q. Ye, D. Yu, M. Yu, X. Zhao, J. Zhou, J. Zhu, S. H. Olsen, J. C. Medina, *J. Med. Chem.* **2014**, *57*, 1454–1472.

[36] Our efforts to incorporate analogous Curtius and Lossen rearrangements (via acyl azides and hydroxamic acids, respectively) into a similar general one-pot procedure have been unsuccessful.

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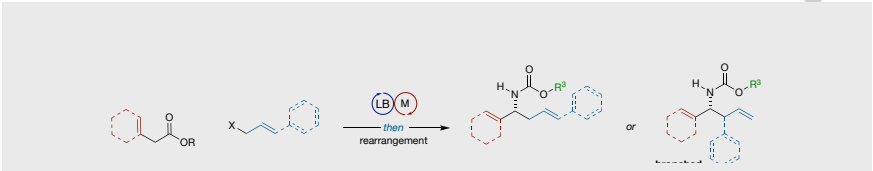

Cooperation then Amination: A unified one-pot experimental protocol enables a versatile regio- and stereodivergent synthesis of homoallylic amines. Critical to the successful development of this method was the recognition that initial catalysed C-C bond formation controls all aspects of reaction regio- and stereoselectivity. Thereafter, *in situ* amination/Hofmann rearrangement results in stereospecific C–N bond formation with attendant control over N-substitution.

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A Regio- and Stereodivergent Synthesis of Homoallylic Amines via a One-Pot Cooperative Catalysis-based Allylic Alkylation/Hofmann Rearrangement Strategy