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Zinc Catalyzed and Mediated Asymmetric Propargylation of Trifluoromethyl Ketones with a Propargyl Boronate

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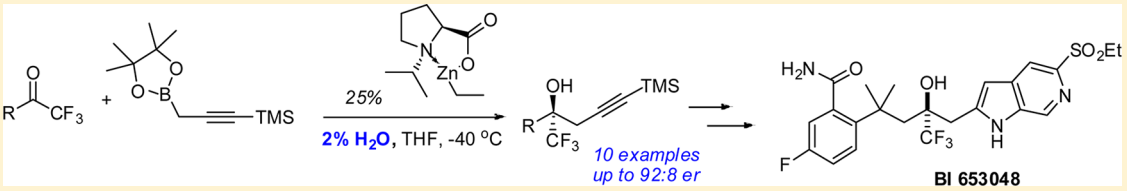
Supporting Information



ABSTRACT: The development of zinc-mediated and -catalyzed asymmetric propargylations of trifluoromethyl ketones with a propargyl borolane and the *N*-isopropyl-L-proline ligand is presented. The methodology provided moderate to high stereoselectivity and was successfully applied on a multikilogram scale for the synthesis of the Glucocorticoid agonist **BI 653048**. A mechanism for the boron−zinc exchange with a propargyl borolane is proposed and supported by modeling at the density functional level of theory. A water acceleration effect on the zinc-catalyzed propargylation was discovered, which enabled a catalytic process to be achieved. Reaction progress analysis supports a predominately rate limiting exchange for the zinc-catalyzed propargylation. A catalytic amount of water is proposed to generate an intermediate that catalyzes the exchange, thereby facilitating the reaction with trifluoromethyl ketones.

INTRODUCTION

Chiral centers that contain a trifluoromethyl substituent have increasingly been incorporated into agricultural, material and medicinal compounds.[1] In the latter application, the pharmacophore was strategically designed into bioactive small molecules for potency, selectivity, biological and physicochemical properties.[1,2] On the basis of these desired attributes, the Glucocorticoid agonist **BI 653048** was designed with a chiral tertiary trifluoromethyl alcohol for the treatment of rheumatoid arthritis.[2a,3] Furthermore, propargylation of carbonyl species[4] provides both an alcohol functional group as well as a synthetically versatile alkyne for derivatization or coupling.[5] Accordingly, the synthesis of **BI 653048** was based on utilizing a chiral homopropargylic trifluoromethyl alcohol intermediate **7a**, which provided an effective handle for a late stage coupling with a suitably functionalized iodopyridine (Scheme 1).[6] After a Sonogashira coupling of the fragments, the eastern azaindole heterocycle was constructed through an *in situ* base-promoted intramolecular cyclization.[7] This two-step sequence enabled a late stage convergent approach toward the development candidate. A resolution-based process for the drug substance was utilized for the first kilogram campaign wherein an α-phenethyl stereocenter was employed to enable the key trifluoromethyl alcohol stereocenter to be established by a late stage selective crystallization from a diastereomeric mixture.[6,8] The zinc-mediated propargylation to furnish the homopropargylic alcohol **7a** proceeded with no diastereoselectivity, but the subsequent crystallization was governed by an eutectic mother liquor composition of approximately 4:1[9] of the undesired to the desired diastereomer **7a**. Accordingly, diastereomerically pure homopropargylic alcohol **7a** was able to be obtained in a single crystallization but the yield was limited to 30−33%. This low yield at an advanced operation became the cost driver and bottleneck for subsequent campaigns. Implementation of a stereoselective propargylation into the process would significantly reduce the raw material cost, number of batches, and waste generated from the beginning of the process through to the advanced intermediate **7a**.[10] On the basis of the homopropargylic alcohol **7a** eutectic controlled crystallization, a projected 3:1 diastereoselectivity for the key propargylation would enable the isolated yield for the key intermediate to be doubled.

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Scheme 1. Initial Development Synthesis of BI 653048

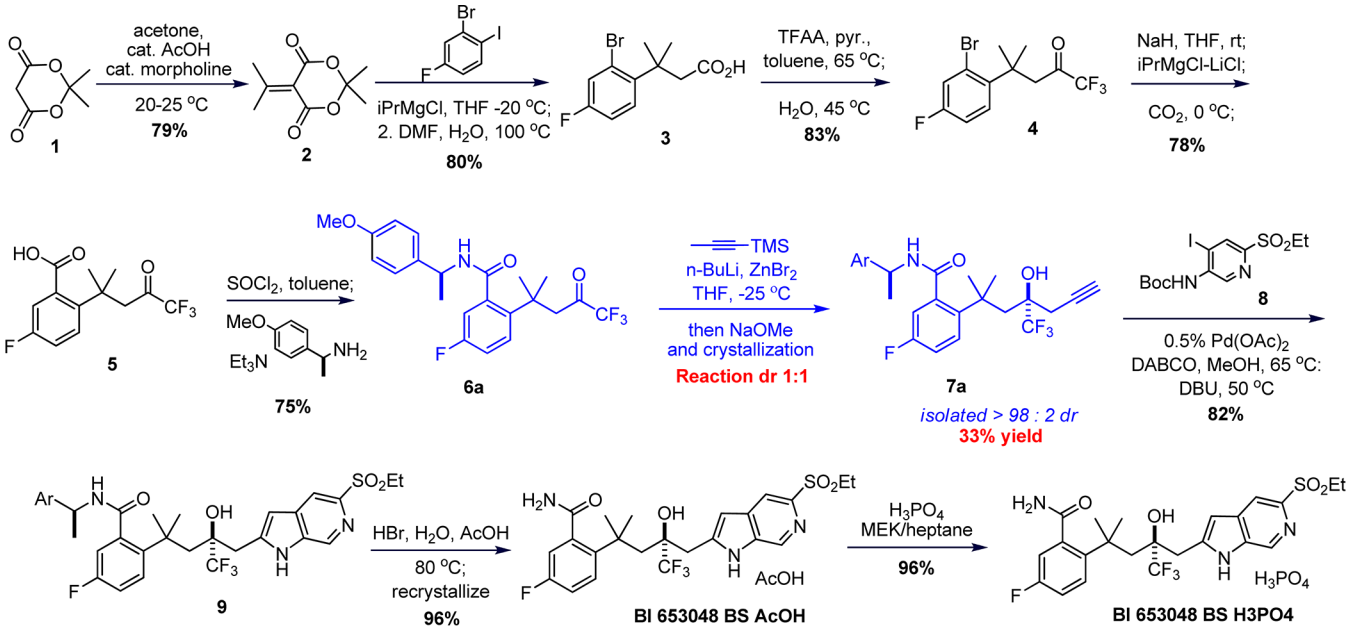
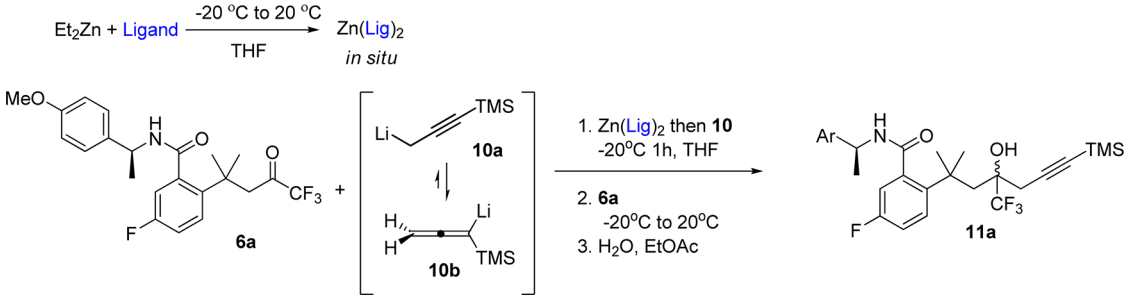
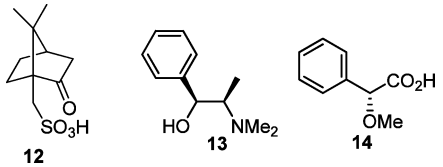


Table 1. Zinc-mediated Asymmetric Propargylation through a di-Ligated Zinc Complex



entry	ligand	$Zn(Lig)_2$:**10** ratio	time,[a] temp	conv.[b]	yield[c]	dr[d]
1	**12**	1	2 h, −20 °C	40%	32%	1.5:1
2	**12**	2	18 h −20 °C	<5%	ND	ND
3	**13**	1	4 h, −25 °C	~17%	ND	1:1
4	**14**	1	1h, −25 °C	~50%	<35%	1:1

[a]Reactions duration until no further conversion was observed. [b]Relative conversion based on mole product/(mole product + mole starting material) determined by HPLC. [c]HPLC assay yield. [d]Diastereomeric ratio determined by HPLC. ND = not determined.



Significant progress has been reported for the asymmetric propargylation of carbonyl compounds.[4,11] In addition to chiral reagent controlled[12] and catalyzed Barbier approaches,[5e,13] catalyzed processes through chiral Lewis acid/base,[14] Cu,[15] Zn,[16] Ir,[17] Cr[5d,18] and organo[19] based catalysts have expanded the substrate scope for asymmetric propargylations. Although reasonably to highly enantioselective asymmetric additions to trifluoromethyl ketones[20,21] including asymmetric allylations[22,23] and organo-zinc additions[22b,24] have been developed, progress on the corresponding asymmetric propargylation has been limited.[13b,25] Only low asymmetric induction has been reported for the necessary propargylation of trifluoromethyl ketones.[26] In order to achieve an economical process toward **BI 653048**, a novel asymmetric propargylation was engineered. Herein, we report the development of a zinc-catalyzed asymmetric propargylation of trifluoromethyl ketones using a propargyl borolane and amino-acid-based ligands.[27]

RESULTS AND DISCUSSION

The first approach toward an asymmetric propargylation of trifluoromethyl ketones was based on chelation of the allenyl zinc reagent utilized in the nonselective propargylation with a suitable chiral ligand. Due to the generally accepted closed 6-membered transition state proposed for zinc-mediated propargylations,[28] chelation of the zinc metal with a chiral

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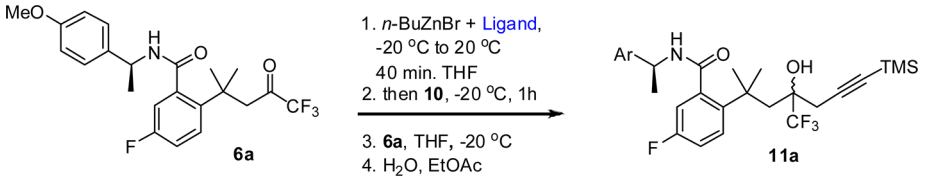
Table 2. Zinc Mediated Asymmetric Propargylation through a Mono-Ligated Zinc Complex



entry	ligand	time,[a] temp	conv.[b]	yield[c]	dr[d]
1	**13**	18 h, −25 °C	68%	53%	1.0:1
2	**14**	18 h, −25 °C	46%	33%	1.0:1
3	**15**	18 h, −25 °C	38%	31%	1.0:1
4	**16**	18 h, −20 °C	53%	43%	1.2:1
5	**16**	4 d, −70 °C	79%	52%[e]	3.1:1
6	**17**	18 h, −25 °C	23%	19%	1.0:1
7	**18**	18 h, −25 °C	89%	78%	1.0:1
8	**19**	18 h, −25 °C	64%	50%	1.0:1
9	**20**	18 h, −25 °C	97%	84%	1.0:1

[a]18 h reaction duration unless otherwise indicated. [b]Relative conversion based on mole product/(mole product + mole starting material) determined by HPLC. [c]HPLC Assay Yield. [d]Diastereomeric ratio determined by HPLC. [e]Isolated yield on a 1g scale and 13% of the allene product was observed.

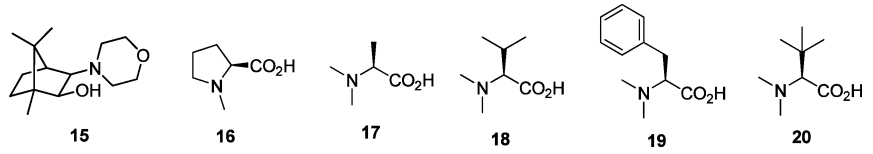
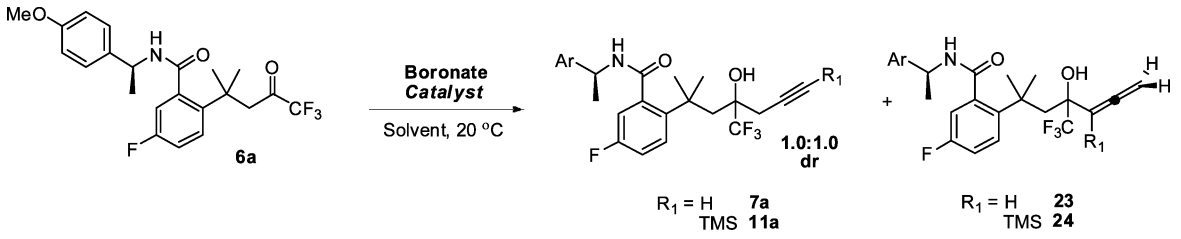


Table 3. Zinc-Mediated and -Catalyzed Propargylations through a B/Zn Exchange[a]



entry	*boronate*	*catalyst*[b]	*conditions*[c]	*conv.*[d]	***7a:23* or *11a:24***[e]
1		*none*	THF, 24h	< 0.5%	ND
2		100% Et_2Zn	THF, <5min	>98%	**97:3**
3	**21**	10% Et_2Zn	THF, <20min	>98%	**94:6**
4		*none*	THF, 24h	<0.5%	ND
5		100% Et_2Zn	THF, 1h	>95%	**80:20**
6		10% Et_2Zn	THF, 3h	>95%	**69:31**
7	**22**	10% Et_2Zn	Tol., 3h	>95%	**19:81**
8		5% Et_2Zn	Tol. 5h	>95%[f]	**5:95**

[a]Reaction performed by charging the borolane (1.5 equiv) followed by the catalyst, if applicable, to a solution of the ketone **6a** in reagent grade THF. [b]Mole percent to ketone **6a**. [c]Reaction duration until no further conversion was observed. [d]Relative conversion based on mole product/(mole product + mole starting material) determined by HPLC. [e]Site selectivity between propargyl and allenyl products determined by HPLC or NMR analysis on the crude reaction mixture. [f]88% Isolated yield. ND = not determined. Tol. = toluene.

ligand should allow a close proximity of the chiral ligand and the addition transition state to facilitate discrimination between the diastereo- or enantiotopic faces of a trifluoromethyl ketone. The initial attempt to generate a chelated zinc complex employed treatment of diethyl zinc with two equivalents of the chiral protic ligands **12**−**14**. The resulting solutions were subsequently treated with the lithiated propyne **10**[29] followed by subjection to the parent substrate **6a** (Table 1). The ligand modified reactions proceeded with only low diastereoselectivity Furthermore, the conversion and ultimate yield were also

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significantly lower than observed for the nonligated process. To address these limitations, an alternative monoligated zinc approach was subsequently pursued.

A monoligated zinc process was explored by treatment of *n*-butyl zinc bromide[30] with stoichiometric chiral protic ligands **13**−**20** prior to the sequential addition of the lithiated propyne **10** and substrate **6a** (Table 2). This approach generally improved the conversion and yield. However, the reaction with amino-alcohol ligands **13** and **15** which are historically employed for ligand-catalyzed and zinc-mediated asymmetric additions of alkynyl, aryl, vinyl and alkyl zinc reagents to aldehydes and ketones[31] provided no diastereoselectivity for the desired propargylation. These results are consistent to the poor enantioselectivity observed with related reagent based zinc-mediated asymmetric propargylations using a stoichiometric chiral amino-alcohol ligand.[32] In an effort to develop a class of ligands that can affect stereoselective induction with a focus on ligands that are economically viable as stoichiometric chiral reagents, a series of per-methylated amino-acids **16**−**20** were examined. The proline based ligand **16** provided a modest but observable degree of diastereoselectivity at −20 °C which improved to 3:1 at −70 °C. The levorotatory ligand **16** favored the desired diastereomer **11a** for application to the drug substance. Although the conversion was improved over the diligated approach, the propargylation under cryogenic conditions necessary for diastereoselectivity afforded only a modest conversion (entry 5).

We recently reported an operationally simple zinc-catalyzed propargylation[33] of aldehydes, ketones and *t*-butanesulfinyl imines[34] with a propargyl boronate based on a boron−zinc exchange mechanism. The catalytic process was anticipated to provide a facile entry into the allenyl zinc reagent necessary for propargylation of the trifluoromethyl ketone **6a**. Similar to the previously reported reactivity, propargyl **21**[35] and allenyl **22** borolanes were unreactive to ketone **6a** at ambient temperature. A rapid and clean propargylation was achieved by subjecting a solution of the borolane and ketone to diethyl zinc (Table 3). Utilizing the propargyl borolane **21**, the propargylation was efficiently catalyzed by diethyl zinc and provided a high conversion and site selectivity for the desired homopropargylic alcohol **11a**. This reactivity was consistent with the proposed two step catalytic cycle based on a B/Zn exchange to generate the allenyl zinc intermediate **25** for a site-selective propargylation (Figure 1).[33,36] The zinc-catalyzed and -mediated addition with the allenyl borolane **22** demonstrated a similar reactivity and site selectivity for allenylation or propargylation based on catalyst loading and solvent choice as we previously reported for the zinc-catalyzed addition with this reagent.[37] These zinc-catalyzed and -mediated propargylations of ketone **6a** through a B/Zn exchange proceeded with no diastereoselectivity but demonstrated a significant improvement in the reaction purity, conversion and yield in comparison to the processes wherein a transmetalation approach was employed to generate the allenyl zinc intermediate.

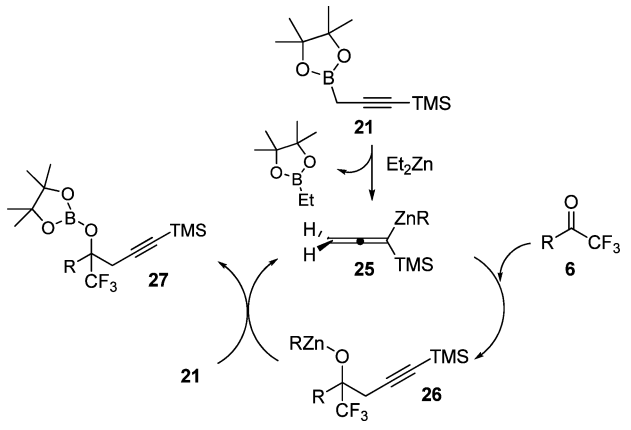

Figure 1. Proposed mechanism for a zinc-catalyzed propargylation of trifluoromethyl ketones with a propargyl boronate.

After demonstrating the rapid and clean propargylation of trifluoromethyl ketone **6a** through a boron−zinc exchange mechanism, this approach served as an efficient platform to optimize the chiral ligand for stereoselective induction. The necessary stoichiometric ligated zinc complexes were prepared by subjecting diethyl zinc to a chiral protic ligand at 40 °C for 3 h prior to the sequential addition of the borolane reagent **21** and ketone substrate **6a** at −20 °C (Table 4). The initially examined ligands were modifications of the initial *N*-methyl-L-proline **16** lead. Variation of the nitrogen substituent showed a significant effect on the diastereoselectivity and achieved a dr of 7:1 (87.5:12.5) to 8.6:1 (89.5:10.5) by employing a *N*-isopropyl **30** or *N*-cyclopentyl **31** substituent respectively (entries 4 and 5). Although the diastereoselectivity was slightly higher with *N*-cyclopentyl-L-proline **31**, the site selectivity for propargylation and ultimate yield was higher for the *N*-isopropyl-L-proline ligand **30**. Further increase in the steric hindrance of the *N*-substituent with a *N*-*t*-butyl group (**33**) significantly reduced the diastereoselectivity to 1.6:1 (entry 7). Modification of the key *N*-isopropyl-L-proline ligand **30** by variation of the pyrrolidine ring to the azetidine **34** or piperidine **35** analogs afforded only low diastereoselectivity (entries 8 and 9). The amino-alcohol analogs to the *N*-isopropyl-L-proline ligand such as the methylene **36**, geminal methyl **37**, and geminal phenyl **38** derivatives (entries 10 to 12) were also examined but furnished only low diastereoselectivity. The amino-alcohol ligands **15** and **39** also provided no diastereoselectivity for the propargylation (entries 13 and 14) similar to the selectivities observed in the transmetalation approaches (Tables 1 and 2). Accordingly, the structural elements of an *N*-isopropyl substituent, carboxylic acid functional group, and pyrrolidine ring within the optimal *N*-isopropyl-L-proline ligand **30** proved essential for stereoselective induction.

The zinc-mediated diastereoselective propargylation with the optimal *N*-isopropyl-L-proline ligand **30** was also examined with the commercially available[38] allenyl borolane reagent **22** (eq 1). Both the diastereoselectivity and site selectivity for propargylation were significantly lower than the corresponding reaction utilizing the propargyl borolane reagent **21**. In addition to the improved selectivities, a large scale process for the propargyl borolane **21** preparation was recently identified allowing for facile access to kilogram scale applications.[35b]

The reaction temperature demonstrated a moderate effect on the diastereoselectivity for the *N*-isopropyl-L-proline ligand **30** modified zinc-mediated propargylation of ketone **6a** employing the propargyl borolane reagent **21**. Increasing the temperature from −20 to 20 °C decreased the diastereoselectivity from 7:1 (88:13) to 3:1 (75:25). The ultimate conversion remained consistent at approximately 79−85% through the examined temperature range albeit the conversion rate was improved by conducting the reaction at a higher temperature. The conversion and diastereoselectivity were dependent on the rate and order of the substrate and borolane addition. For

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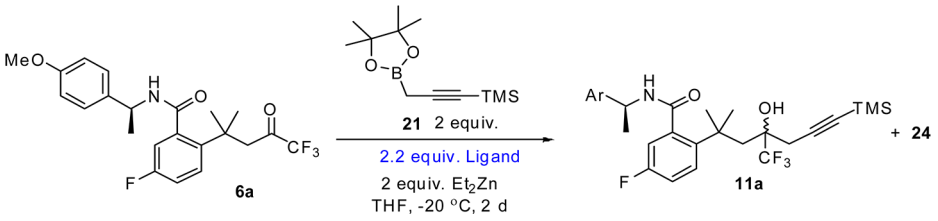
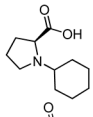
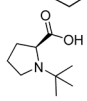
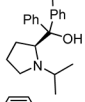
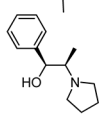
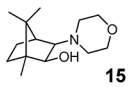
Table 4. Ligand Screen for the Diastereoselective Propargylation of Ketone 6a[a]



entry	*ligand*	*conv.*[b]	***11a*:24**[c]	***11a dr***[d]
1	 **16**	98%	11:1	1.5:1
2	 **28**	90%	10:1	2.9:1
3	 **29**	96%	10:1	2.1:1
4	 **30**	85%	15:1	7.0:1
5	 **31**	90%	7:1	8.6:1
6	 **32**	93%	7:1	7.0:1
7	 **33**	93%	11:1	1.6:1
8	 **34**	36%	11:1	1.4:1
9	 **35**	96%	13:1	1.2:1
10	 **36**	>96%	19:1	1.1:1
11	 **37**	>96%	16:1	1.0:1
12	 **38**	>96%	19:1	1.6:1
13	 **39**	100%	3:1	1.0:1
14	 **15**	100%	1.4:1	1.0:1

[a]Reactions performed by the sequential charge at −20 °C of the borolane **21** followed by a THF solution of the ketone **6a** to an aged solution of diethyl zinc and ligand in reagent grade THF. [b]Two day reaction duration regardless of conversion. Relative conversion based on mole product/(mole product + mole starting material) determined by HPLC. [c]HPLC area ratio. [d]Diastereoselectivity determined by HPLC.

reasonable diastereoselectivity at ambient temperature, a solution of the borolane reagent **21** and ketone substrate **6a** must be charged to a solution of the pregenerated ligated zinc complex. The reverse addition afforded a lower 2:1 dr. With the appropriate addition order, the diastereomeric ratio increased to 3.6:1 by conducting a 10 h metered addition (Table 5). Minimal impact on the site selectivity was observed by modification of the addition time. The diethyl zinc and chiral ligand loadings were also reduced from 2 to 1.2 equiv while retaining the conversion and diastereoselectivity by employing the metered addition (entries 4 and 5). However, the stoichiometry between zinc and the chiral ligand was critical for stereoselective induction. A 10 mol % excess of diethyl zinc to the chiral ligand afforded a rapid and clean propargylation but proceeded with no diastereoselectivity (entries 6) indicative of a facile and competitive nonligated background reaction *vide*

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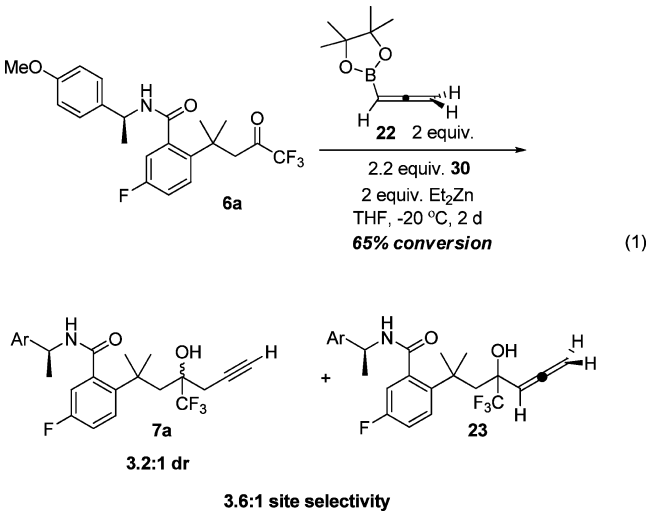
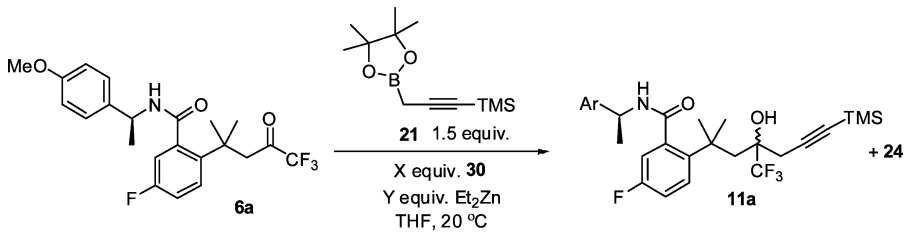


infra. Accordingly, the stereoselective propargylation was designed to utilize a slight excess of the chiral ligand to zinc. Further reduction in the zinc and ligand loadings afforded irreproducible results wherein the conversion and diastereoselectivity varied between batches. The optimal ambient temperature conditions for the zinc-mediated diastereoselective propargylation employed 1.23 equiv of the chiral ligand **30** and 1.20 equiv of diethyl zinc relative to the ketone substrate and a 5−10 h addition of the trifluoromethyl ketone substrate **6a** and borolane **21** to the pregenerated ligated zinc complex. These conditions for the stereoselective propargylation reproduced well on multikilogram scales (Table 6). The preparative process utilizing the optimal conditions aged the batch for at least 3 h after the metered addition. The bulk of the zinc salts[39] and ligand were subsequently removed by an aqueous hydrochloric acid wash. Proto-desilylation of intermediate **11a** was accomplished by treatment with a methanol solution of sodium methoxide at 35 °C for 1h. Diastereomerically pure (>99:1 dr) homopropargylic alcohol **7a** was ultimately isolated after workup and a eutectic controlled crystallization in isopropyl acetate and heptane. Through 2 kilolaboratory and 10 pilot plant batches, 242 kg of the trifluoromethyl ketone **6a** were subjected to the optimized conditions to provide 180 kg of the key diastereomerically pure homopropargylic alcohol **7a** in an overall yield of 68% wherein the key propargylation proceeded with a weighted average of a 78:22 diastereomeric ratio. Overall, the principal objective to double the isolated yield for the key operation was achieved by utilizing an *N*-isopropyl-L-proline **30** modified zinc-mediated propargylation.

Further review of the scaleup batches showed variation in the conversion and reaction diastereoselectivity (Table 6). The diastereoselectivity varied between 75:25 (3:1) to 81:19 (4.3:1). Although most of the batches achieved >95% conversion, the final batch (entry 12) proceeded to 90% conversion after agitation for 12 h after the substrate addition. These combined factors resulted in variation of the isolated yield between 58 and 75% for the isolated diastereomerically pure homopropargylic alcohol **7a** indicating that an unknown factor influenced both the conversion and diastereoselectivity for the zinc-mediated propargylation. Processes that are advanced to a pilot plant scale are examined for robustness, and factors that can reasonably affect the process are examined and the appropriate specifications established.[40] Due to the organo-metallic nature of the propargylation, the reaction tolerance for water was proactively determined, and up to 2000 ppm water in the THF solvent showed no impact on the process. This level is four times the <500 ppm specification for reagent grade THF that is routinely employed in the pilot plant. However, trace amounts of water proved essential for good conversion, reaction rate and diastereoselectivity (Table 7). Under as dry as possible conditions,[41] a 45% conversion and 65:35 dr was obtained for the propargylation at 30 min after the metered addition which improved to 89% conversion and 70:30 dr at 18 h. Addition of 4 to 18 mol % percent water relative to the trifluoromethyl ketone **6a** enabled complete conversion and optimal diastereoselectivity (>80:20) within 30 min after the metered addition. This amount of water is equivalent to 185 to 837 ppm water in the THF solvent.[42] The water additive must also be charged to the ligated zinc complex after its formation

Table 5. Metered Addition and Zinc-Ligand Stoichiometry Optimization[a]



entry	addition time (h)	X (equiv) **30**	Y (equiv) Et_2Zn	conv.[b]	**11a**:**24**[c]	**11a** dr[d]
1	1.5	2.2	2.0	85%	20:1	2.8:1
2	5.2	2.2	2.0	96%	20:1	3.5:1
3	10.4	2.2	2.0	>98%	>25:1	3.6:1
4	10	2.2	2.0	>98%	>25:1	3.6:1
5	10	1.23	1.20	>99%	22:1	4.0:1
6	10	1.23	1.33	>99%	>30:1	1.0:1
7	10	1.23	1.50	>99%	>30:1	1.0:1

[a]Reactions were performed by the metered addition at the indicated interval of a ketone **6a** and borolane **21** THF solution to an aged (40 °C for 3 h) solution of diethyl zinc and ligand **30** in reagent grade THF at 20 °C. Equivalents of zinc and ligand are relative to ketone **6a**. [b]Reactions were run for 12 h regardless of conversion. Relative conversion based on mole product/(mole product + mole starting material) determined by HPLC. [c]HPLC Area ratio. [d]Diastereoselectivity determined by HPLC.

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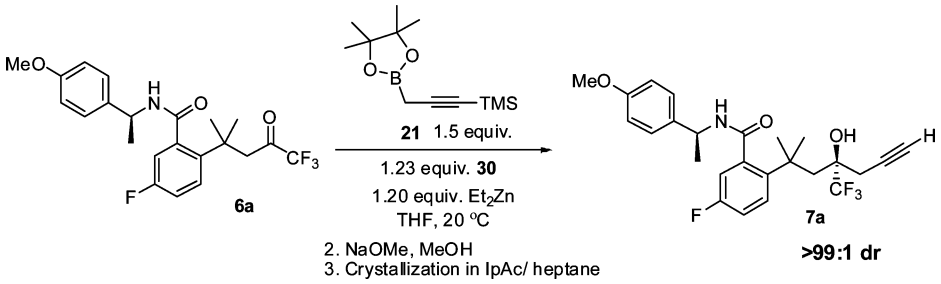
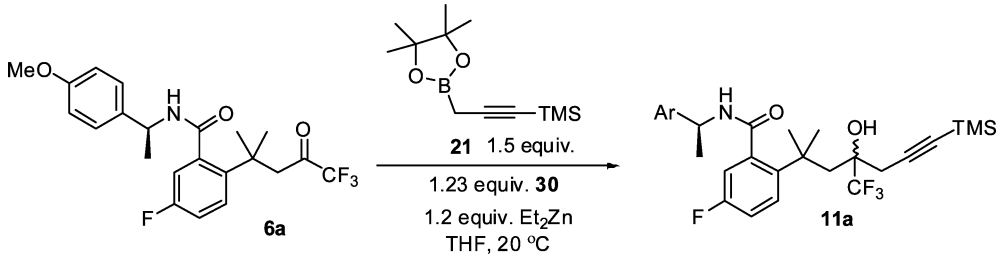
Table 6. Kilogram Scaleup of the Zinc-mediated Stereoselective Propargylation[a]



entry	input **6a** (kg)	reaction **11a** dr[b]	output **7a** (kg)	yield[c]	quality[d] (wt%)
1	1.0	75:25	0.8	65%	99
2	3.6	77:23	2.7	68%	98
3	25	81:19	18	64%	98
4	25	79:21	19	69%	99
5	25	80:20	19	68%	99
6	25	80:20	20	71%	98
7	13	80:20	10	72%	99
8	13	81:19	11	75%	99
9	10	77:23	7	64%	97
10	34	75:25	24	66%	99
11	34	79:21	26	68%	98
12	34	75:25	22	58%	97

[a]Reactions performed by the metered addition over 5−10 h of a ketone **6a** and borolane **21** THF solution to an aged (40 °C for 3h) solution of diethyl zinc and ligand **30** in reagent grade THF at 20 °C. Reactions were run for 3 to 12 h. [b]Diastereoselectivity determined by HPLC of the crude propargylation reaction before workup. [c]Isolated yield of diastereomerically pure **7a** after crystallization. [d]Quality by weight percent determined by 1H NMR assay with dimethyl fumarate or by calibrated HPLC assay.

Table 7. Water Effect on the Zinc-mediated Diastereoselective Propargylation of 6a[a]



entry	water[b]	30 min conv.[c]	18 h **11a** dr[d]	conv.[e]	**11a** dr[d]
1	0%	45%	65:35	89%	70:30
2	0.5%	59%	71:29	94%	73:27
3	4%	>99%	81:10		
4	8%	>99%[f]	82:18		
5	14%	>99%	80:20		
6	18%	98%	81:19		
7	40%	91%	75:25	96%	80:20
8	70%	75%	71:29	92%	75:25
9	100%	36%	ND	35%	ND

[a]Reactions performed by the metered addition over 5 h of an anhydrous ketone **6a** and borolane **21** THF solution to an aged (40 °C for 3 h) solution of diethyl zinc, ligand **30**, and the indicated amount of water in anhydrous THF at 20 °C. [b]Mol percent water relative to starting ketone **6a**. [c]Relative conversion at 30 min after the metered addition. [d]Diastereoselectivity of the crude propargylation reaction before workup determined by HPLC. [e]Relative conversion at 18 h after the metered addition. [f]74% isolated yield of diastereomerically pure **7a** was obtained after proto-desilylation and crystallization. ND = not determined.

for a water effect to be observed. Therefore, employing a catalytic amount of water allowed a slight improvement in the stereoselectivity with a more significant impact on the rate of the reaction.

The catalyst loading was able to be lowered and a zinc-catalyzed stereoselective propargylation achieved by the addition of catalytic water due to the resulting improvement in the reaction rate. The catalyst loading and stoichiometry between the ligated zinc catalyst and water were optimized through a 2D design of experiment (DoE) approach with ketone **6a** (Figure 2).[43] The design focused on a catalytic process with the factors of catalysts loading (1 to 40 mol %) and water (1 to 40 mol %) for the dimensions and employed a 3 h addition of the substrate **6a** and borolane **21** to a solution

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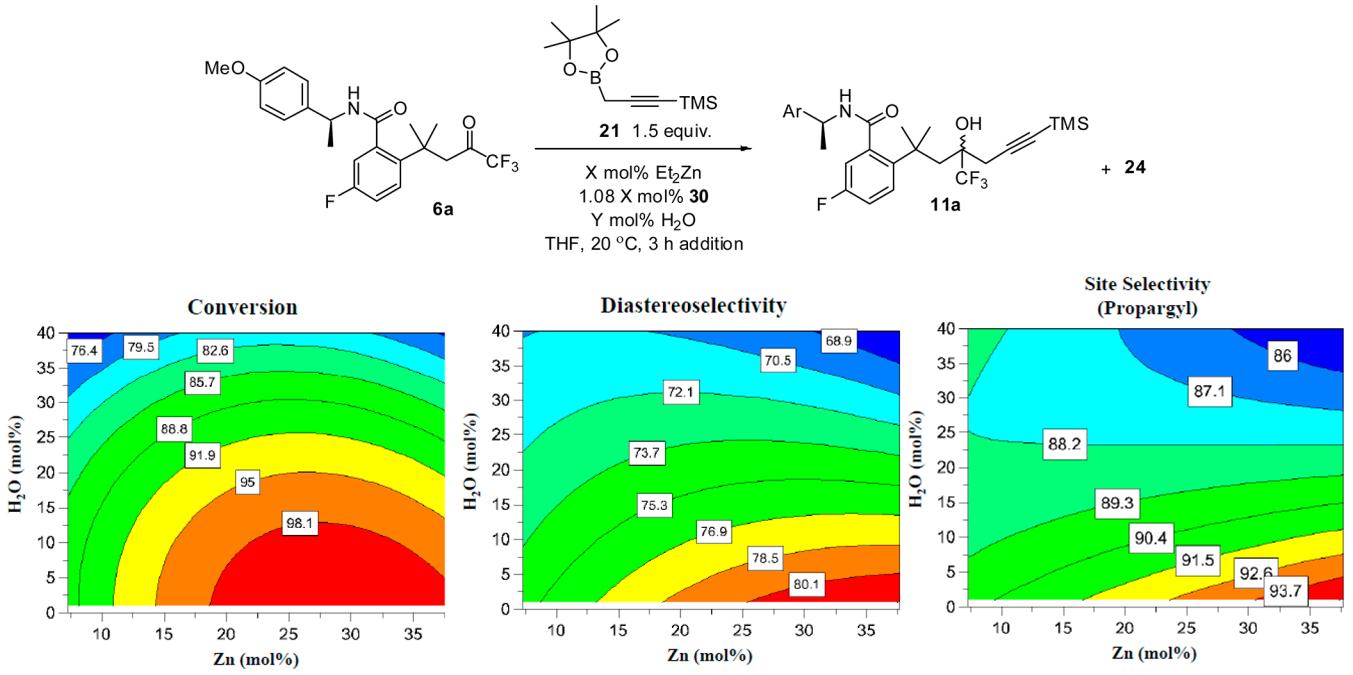
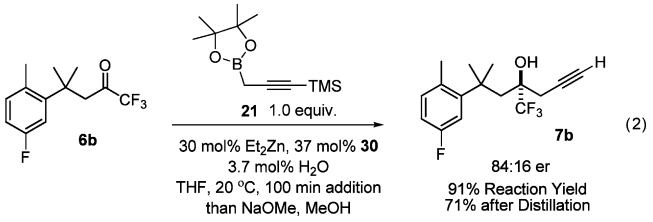


Figure 2. DoE optimization for the zinc-catalyzed diastereoselective propargylation of ketone **6a**. Reactions performed by the metered addition over 3 h of an anhydrous ketone **6a** and borolane **21** THF solution to an aged (40 °C for 3 h) solution of diethyl zinc, ligand **30** and water in anhydrous THF as the indicated stoichiometry and 20 °C. Reactions progressed for 10 h at which point the conversion, diastereoselectivity (normalized), and site selectivity (normalized) were determined by HPLC.

of the pregenerated chiral zinc complex. The observable responses which were optimized are those that directly affect the yield, namely the conversion, diastereoselectivity and site selectivity after a 10 h reaction. The optimal conditions for all three parameters were related to moderate zinc catalyst loadings (25−40 mol %) with a low water content (~2 mol %). The lowest optimal catalyst loading was 25 mol % zinc catalyst with 2 mol % water to provide 99% conversion, 80:20 diastereoselectivity, and 92:8 site selectivity for the propargylation of ketone **6a** at ambient temperature.

A parallel optimization of the catalyst loading and water was conducted for the asymmetric propargylation of the trifluoromethyl ketone **6b**, and a similar catalyst (30 mol %) and water (3.7 mol %) loading were found for optimal conversion and enantioselectivity. The asymmetric propargylation of the ketone **6b** on a 70 g scale at ambient temperature with these catalytic conditions afforded a 91% reaction yield and 84:16 er for the homopropargylic alcohol **7b** after proto-desilylation (eq 2).



(2)

The stereoselectivity for the optimized zinc-catalyzed propargylation was improved under cryogenic conditions. The diastereoselectivity for the parent system improved to 9:1 dr by conducting the zinc-catalyzed propargylation at −40 °C (Table 8). Complete conversion was able to be achieved at −40 °C due to the improved reactivity by the addition of catalytic water to the process. Reactions at lower temperatures lead to incomplete and irreproducible conversions. The optimal conditions for the catalytic stereoselective propargylation of trifluoromethyl ketones with propargyl borolane **21** employed 25 mol % of diethyl zinc, 27 mol % amino-acid **30**, and 2 mol % water with a −40 °C reaction temperature

The optimized zinc-catalyzed asymmetric propargylation of trifluoromethyl ketones proved reasonably general, tolerating both aliphatic and aromatic substrates (Table 9). The enantioselective propargylation of the achiral analogs **6b**, **6c**, **6d**, **6e**, and **6f** afforded a nearly identical degree of asymmetric induction (89:11 to 93:7 er) as compared to the parent system (90:10 dr) (entries 1−6). The asymmetric induction was therefore predominately due to the ability of the *N*-iPr-L-Pro ligand to discriminate the enantiotopic or diastereotopic ketone faces with a minimal influence from the α-phen-ethyl stereocenter of the parent chiral ketone **6a**.[44] Furthermore, the process proved compatible with halides, thioethers, and Lewis basic amide functional groups. The asymmetric propargylation of the aromatic trifluoromethyl ketones **6g**, **6h**, and **6i** provided 81:19 to 86:14 enantiomeric ratios with no apparent influence by a para-electronically donating or slightly electron withdrawing substituent (entries 7−9). The analogous aliphatic substrate to the parent system without the neopentyl fragment also afforded a high yield with only a slight decrease in enantioselectivity (entry 10). In general, the zinc-catalyzed asymmetric propargylation provided an operationally simple process for the construction of chiral homopropargylic trifluoromethyl alcohols.

The key observation that enabled the catalyst loading to be lowered for a catalytic process was the inclusion of catalytic water to the reaction. To further define this effect, the reaction rate profile for the zinc-catalyzed asymmetric propargylation was examined. The reaction with the parent system demonstrated significant rate acceleration with 2 mol % water (Figure 3). The reaction with catalytic water was complete in 1

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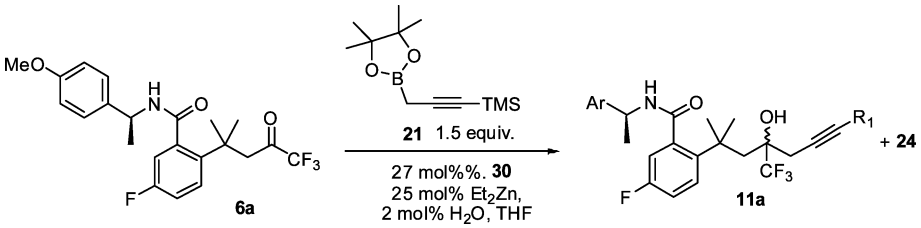
Table 8. Temperature Effect on the Zinc-catalyzed Diastereoselective Propargylation of 6a[a]



entry	temp.[b] (°C)	time[c] (h)	conv.[d]	dr 11a[e]	11a:24[e]
1	20	5	>98%	4−4.4:1	15:1
2	0	10	>98%	5:1	14:1
3	−20	42	98%	6:1	14:1
4	−40	48	>98%	9:1	19:1

[a]Mole percent ligand **30**, diethyl zinc and water to the starting ketone **6a**. Reactions performed by the metered addition over 5 h of an anhydrous ketone **6a** and borolane **21** THF solution to an aged (40 °C for 3 h) solution of diethyl zinc, ligand **30** and water in anhydrous THF at the indicated temperature. [b]Reaction temperature for the zinc-catalyzed propargylation. [c]Time until >97% molar conversion. [d]Relative conversion. [e]Diastereoselectivity and site selectivity determined by HPLC.

h, and the anhydrous reaction required over 3 h when 1.7 equivalents of the borolane **21** were employed and the reaction conducted at 20 °C.[41] With 2 mol % water, the reaction rate initiated at a TOF of 10/h and gradually decreased as the reaction progressed. Without water, the reaction demonstrated a slow induction phase to peak at a rate of TOF 1.8/h. Catalytic water in the diastereoselective propargylation eliminated the induction phase of the reaction and increased the peak reaction rate by over 500%.

The influence of water on the nonligated and more facile zinc-catalyzed propargylation was also examined by comparing the peak reaction rate with and without catalytic water for reaction with the aldehyde **40**, methyl ketone **41** and parent trifluoromethyl ketone **6a** (Table 10). Initial analysis revealed a significant rate difference among the substrates. The zinc-catalyzed nonligated propargylation of *p*-anisaldehyde **40** achieved a TOF of >10000/h wherein complete conversion was obtained in less than 1 min with only 2 mol % diethyl zinc. The acetophenone **41** substrate showed an approximate 15-fold decrease in the peak reaction rate over the aldehyde. The peak reaction rate for the parent trifluoromethyl ketone **6a** was approximately 10-fold decrease over that of the methyl ketone **41**. For the methylketone **41** and trifluoromethyl ketone **6a** substrates wherein an accurate reaction rate could be measured, the influence of 1 mol % water on the zinc-catalyzed (2 mol %) propargylation increased the peak reaction rate by approximately 20%. Furthermore, comparison of the peak reaction rates for the diastereoselective ligated zinc-catalyzed propargylation with 25 mol % catalyst (Figure 3) to the nonligated and unselective zinc-catalyzed propargylation with 2 mol % catalyst (Table 10) showed that the nonligated TOF was approximately 800% higher than the slower amino-acid ligated reaction. Accordingly, the zinc-catalyzed propargylation was ligand decelerating. Catalytic water influenced the reaction rate in both the ligated and nonligated zinc-catalyzed propargylations, and the influence was more significant in the slower ligated asymmetric process.

A reasonable mechanistic rationalization for the influence of water on the rate of the zinc-catalyzed propargylation relates to water facilitating the rate limiting step in the catalytic cycle (Figure 1). The catalyst behavior was qualitatively determined by application of Blackmond's reaction progress analysis[48] on the nonligated zinc and water-catalyzed propargylation with the slower parent trifluoromethyl ketone substrate **6a** by employing different excesses between the substrate and borolane reagent **21** (Figure 4). No overlay between all the examined excesses were observed in the graph analysis relating the reaction rate to the substrate concentration or time as well as relating the reaction rate divided by the borolane concentration to the substrate concentration (Graphs a-c). However, an overlay between the reaction rate divided by the borolane concentration was observed between reactions with the same initial substrate concentration (Graph c). The reaction rate under this relationship showed a minor negative slope for approximately 75% of the reaction which changed slope and behavior when less than 25% of the substrate remained. This pattern is indicative of the rate limiting operation for the first approximate 75% of the reaction dependent on the borolane concentration, i.e. exchange, then changing to the substrate concentration, i.e. addition, when the substrate concentration decreases to become rate limiting. The reaction rate divided by the borolane concentration at less than 75% conversion increased with decreasing substrate concentration indicative of product acceleration or starting material inhibition. Zinc complexes and reactions are routinely influenced by the aggregation of the zinc intermediates in solution.[49] A reasonable rationalization for this reaction rate behavior relates to the product facilitating the deaggregation of the zinc complexes and thereby affording a slight rate increase with increasing product concentration. A well fit overlay regardless of the initial substrate concentration was observed when the reaction rate divided by the borolane concentration was compared to the product concentration (graph d). No clear kinetic information could be ascertained with different concentrations of water or zinc or through examination of the asymmetric ligated process. However, the graph analysis for the reaction progress analysis supported the exchange as the principal rate limiting operation while the influence of the product contributes a minor component to the reaction rate. Therefore, catalytic water reasonably led to an acceleration of the predominately rate limiting exchange within the zinc-catalyzed propargylation.

In order to address the water effect on the zinc-catalyzed propargylation, a mechanistic rationalization for the key rate limiting B/Zn exchange must be formulated. Since the pioneering work of Zakharkin and Okhlobystin and Thiele and co-workers,[50] the B/Zn exchange has led to general access

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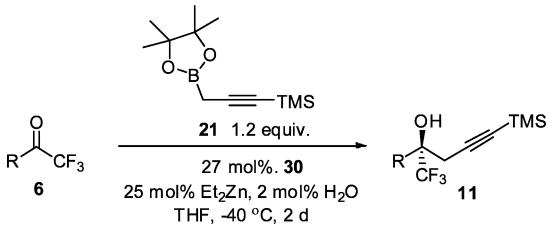
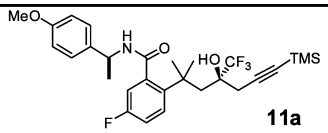
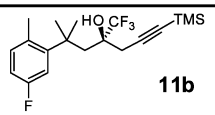
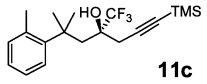
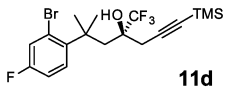
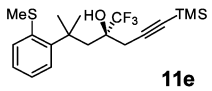
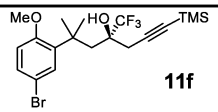
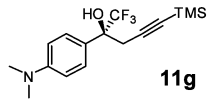
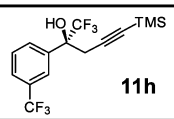
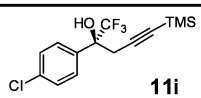
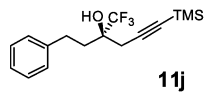
Table 9. Substrate Scope for the Zinc-catalyzed Stereoselective Propargylation[a]



entry	*product*	*dr or er*[b]	*yield*[c]
1	 **11a**	90:10[d]	78%
2	 **11b**	90:10[e]	90%
3	 **11c**	92:8	90%
4	 **11d**	89:11	75%
5	 **11e**	93:7	84%
6	 **11f**	91:9[e]	94%
7	 **11g**	86:14	91%
8	 **11h**	81:19	83%
9	 **11i**	85:15	70%
10	 **11j**	80:20	89%

[a]Reactions performed by the metered addition over 3−6 h of an anhydrous ketone and borolane **21** THF solution to an aged (40 °C for 3 h) solution of diethyl zinc, ligand **30** and water in anhydrous THF at −40 °C. [b]Enantiomeric ratio determined by Chiral HPLC.[45] Absolute stereochemistry assigned by analogy to the diastereoselective propargylation of trifluoromethyl ketone **6a**. [c]Isolated yield. [d]Diastereomeric ratio determined by HPLC. [e]Enantiomeric ratio determined by chiral HPLC after proto-desilylation.

to organo-zinc complexes.[51] Several mechanisms for B/Zn exchanges have been derived from DFT calculations[52] wherein the formulated exchange mechanisms between organozinc complexes and organoboronate esters involve coordination of the organozinc complex to the boronate oxygen to promote a ligand transfer from zinc to boron and activate the system for the exchange through a boron "ate" intermediate.[52c−e] Alternatively, six membered chairlike transition states with inversion for the exchange of allyl borolanes with zinc fluoride or alkoxy complexes have been proposed based on experimental observations.[53] Two observations from our previous publications on zinc-catalyzed additions based on a B/Zn exchange should be rationalized by the transition state for the key exchange involved in the zinc-catalyzed propargylation.

dx.doi.org/10.1021/jo400080y | J. Org. Chem. 2013, 78, 3592−3615

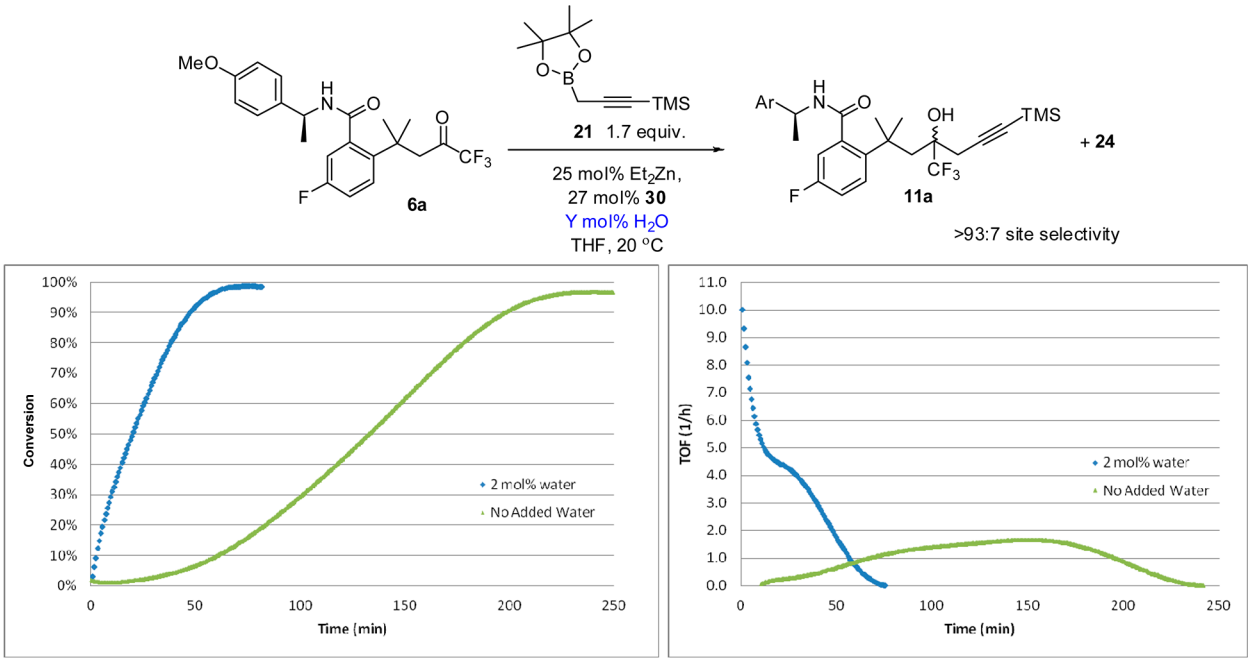
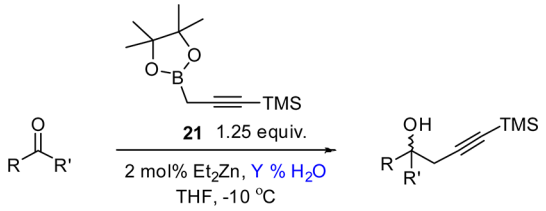
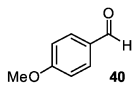
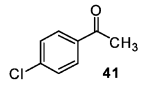
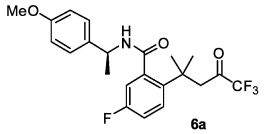


Figure 3. Water effect on the reaction rate for the zinc-catalyzed diastereoselective propargylation of trifluoromethyl ketone **6a**.[46] Reaction performed by charging an aged (40 °C for 3 h) solution of diethyl zinc and ligand **30** in anhydrous THF to an anhydrous THF solution of the borolane **21**, ketone **6a** and the indicated amount of water at 20 °C. Total concentration was 0.30 M borolane **21** and 0.18 M ketone **6a**. Relative reaction conversion monitored by React IR. Turnover Frequency (TOF) of the catalyst was per hour.

Table 10. Water Effect on the Reaction Rate for the Zinc-catalyzed Propargylation[a,41,47]



	peak TOF (h^{-1})	
substrate	*without water*	*1 mol% water*
 **40**	>10,000[b]	ND
 **41**	641	765
 **6a**	66	80

[a]Reaction performed by charging diethyl zinc (2 mol % relative to substrate) in one portion to a solution of the substrate (0.3 M) and borolane **21** (0.38 M) at −10 °C in anhydrous THF with the indicated amount of water. Reaction progress monitored by React-IR. See Supporting Information for conversion and rate profile in relation to time. [b]Rate exceeded accurate measurement by React-IR and was complete in less than 1 min. Reaction rate was at least 10000 TOF, and the temperature rose to 6 °C during the reaction. ND = Not determined.

First, our zinc-catalyzed allenylation of aldehydes and ketones with an allenyl boronate **22** demonstrated a highly selective inversion process for the B/Zn exchange which was also consistent for reactions with a propargyl boronate reagent.[37] Second, our zinc-catalyzed allylation of ketones with an allyl borolane reagent demonstrated an increased exchange activity for an alkoxy zinc complex in comparison to diethyl zinc toward the allyl borolane, and the allylation reaction required an alcohol additive with catalytic diethyl zinc for reactivity.[53b] To account for these observations as well as maintain the requirement of a boron "ate" intermediate necessary to activate the migration of the organo-ligand from boron to zinc,[52] a reasonable exchange mechanism relates to boron coordination to the zinc alkoxide ligand to directly position the system for a closed six membered based B/Zn exchange transition state (Figure 5). Accordingly, a Lewis acid−Lewis base interaction[54] can initiate a feasibly concerted and facile inversion based exchange to directly generate the allenyl zinc intermediate **25**.

A computation assessment on the proposed closed 6-membered based B/Zn exchange with a propargyl boronate and a model system supported a smooth inversion based intramolecular mechanism. Computation analysis was performed on a high performance computer with Gaussian 09[55] software at the density functional level of theory and employed the B3LYP method and LANL2DZ bases set. All structures were optimized, and the coordinated starting material and product showed no imaginary frequencies. The proposed exchange transition state showed one imaginary frequency and a vibration mode consistent with the expected transition state (Figure 6). Subsequent IRC plots demonstrated a smooth connection between the starting material **42**, transition state **43**, and product **44**. The low calculated barrier for the exchange was consistent to the facile zinc-catalyzed propargylation observed at or below room temperature. Furthermore, an equilibrium[52a,b,e] between the starting material and allenyl zinc

dx.doi.org/10.1021/jo400080y | J. Org. Chem. 2013, 78, 3592−3615

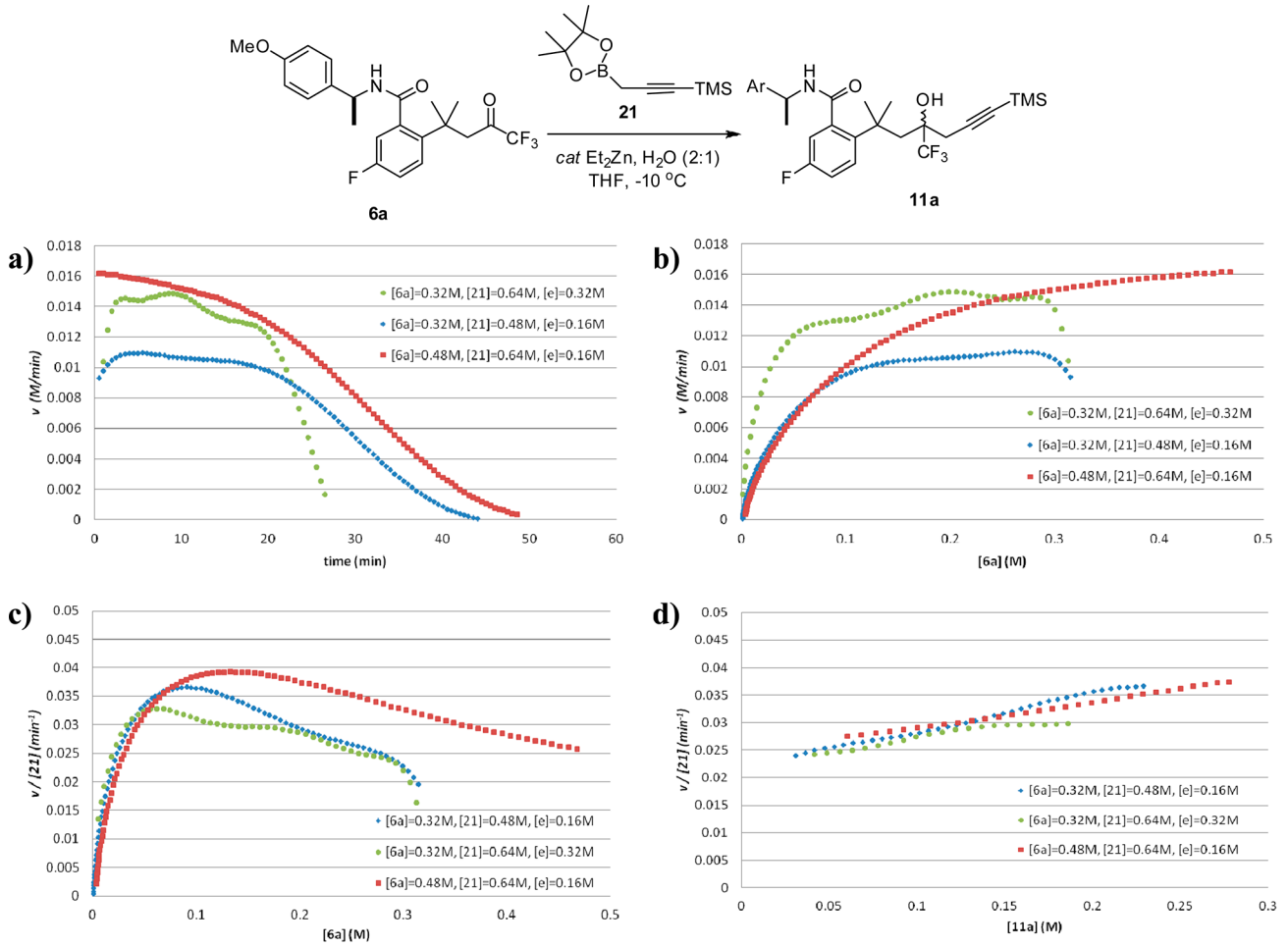


Figure 4. Reaction progress analysis for the zinc-catalyzed propargylation of ketone **6a**. Reactions performed by charging diethyl zinc $[Et_2Zn]$ = 0.0064 M to a solution of the ketone **6a**, borolane, and water $[H_2O]$ = 0.0031 M in anhydrous THF at −10 °C. Reaction progress monitored by React IR and analyzed after fitting to a 10th order polynomial regression.

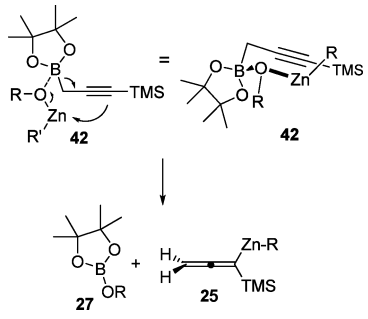


Figure 5. Plausible closed 6-membered based B/Zn exchange with a propargyl boronate.

intermediate was apparent wherein the starting coordinated species **42** was slightly favored over the coordinated allenyl zinc intermediate **44**. The direction of the equilibrium between the dissociated starting and product species will be dependent on the complexation, solvation, and dissociated adduct energies[56] but will ultimately be driven to the allenyl zinc intermediate as the allenyl zinc intermediate is consumed during the reaction progression. Competitive mechanisms for the B/Zn exchange can not be excluded, but the formulated B/Zn exchange which was initiated by a Lewis-acid and Lewis-base interaction provided a simple rationalization for the key facile exchange.

Catalytic water has historically been observed to influence the rate of numerous reactions.[57] The effect on zinc-mediated additions is precedented but not well characterized nor provided for an apparent rationalization for the exchange acceleration observed for the zinc-catalyzed propargylation.[57,58] In the proposed closed 6-membered based exchange mechanism, a coordination between the boron reagent and the zinc alkoxide product derived from the propargylation is required to initiate the exchange. Accordingly, the electronic and steric properties of the zinc alkoxide ligand are expected to influence the rate of the exchange. Larger alkoxide ligands would hinder the key coordination to the boron reagent. Additionally, electronically deficient alkoxide ligands would decrease the Lewis basicity of the zinc alkoxide complex and also impede the key coordination. The tertiary and electronically deficient zinc alkoxide products derived from propargylation of trifluoromethyl ketones are expected to be poor intermediates for the B/Zn exchange as demonstrated by the decreased reaction rate in comparison to the aldehyde or methyl ketone substrates. Furthermore, increasing the steric environment around the zinc metal with a chiral ligand would further inhibit the key boron to zinc alkoxide interaction and account for the observed ligand deceleration for the stereoselective process. A reasonable rationalization for the water influence on the zinc-catalyzed propargylation relates to water generating an intermediate which can catalyze the rate limiting

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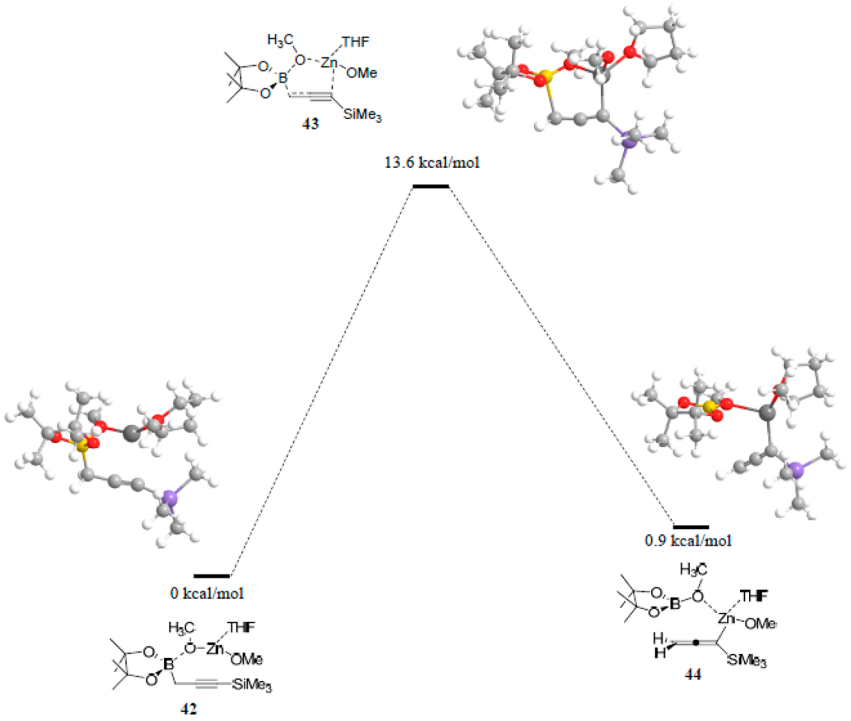
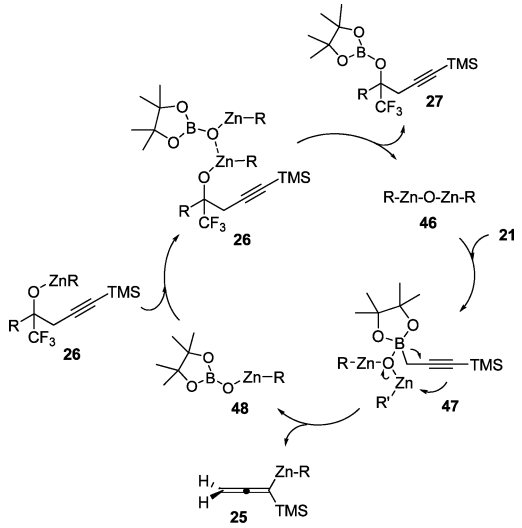


Figure 6. Calculated reaction coordinate for a closed 6-membered based B/Zn exchange with a propargyl boronate.

exchange (Scheme 2).[59] Treatment of an organo-zinc complex with water is expected to generate a zinc hydroxide or dinuclear

Scheme 2. Proposed Catalytic Cycle for the B/Zn Exchange with a Dinuclear Zinc Oxo-Complex



zinc oxo-complex **46**, which have previously been demonstrated as competent species for a B/Zn exchange,[60] and produce the allenyl zinc intermediate **25** and a boro-oxo-zinc byproduct **48** after an exchange. This resulting adduct **48** can undergo a subsequent alkoxide ligand exchange[52b] with the alkoxide zinc product **26** derived from the propargylation of a trifluoromethyl ketone substrate to regenerate the dinuclear zinc oxo-complex **46** and complete a catalytic cycle. Direct detection of the key intermediates or elucidation of the rate order for zinc and water for the catalyzed propargylation proved challenging due to the complex mixture of zinc complexes present in the reaction. However, the model predicted that pinacol boronic acid, due to the expected facile reaction with an organo-zinc intermediate to generate the key boro-oxo zinc intermediate **48**, should have a similar effect on the rate of the propargylation as water. Nearly identical conversions, rate and rate profiles for both the ligated and nonligated zinc-catalyzed propargylations were observed with equal catalyst loading of pinacol boronic acid[61] and water (Figure 7 and 8) to support adduct **48** as a viable intermediate. Additionally, catalytic pinacol boronic acid eliminated the induction phase of the ligated zinc-catalyzed stereoselective propargylation as observed with catalytic water. Therefore, a parallel catalytic process[62] initiated by catalytic water or pinacol boronic acid reasonably accelerated the rate limiting boron–zinc exchange within the zinc-catalyzed propargylation (Scheme 3).

An alternative experiment was designed to demonstrate multiple mechanisms for the zinc and water-catalyzed propargylation based on sequential charges of the propargyl borolane to an excess of the trifluoromethyl ketone substrate **6a** wherein the experiment was designed to operate in the rate limiting exchange phase of the reaction (Figure 9). The reaction rate was monitored by calorimetry under isothermal conditions. In each of the sequential 7 mol % borolane **21** additions to the ketone substrate **6a**, a rapid reaction was initially observed which proceeded to an apparent first order decay based on the borolane as the limiting reagent. The reaction behavior supported a highly active catalyst adduct accumulation after completion of a proceeding segment which induced a rapid initial reaction at the subsequent borolane **21** charge. After consumption of the highly active intermediate, a steady state catalytic cycle progressed until the borolane reagent was consumed. This two phase reaction profile under sequential borolane **21** charges would not be consistent with a reaction behavior involving a catalyst resting state at the zinc alkoxide product **26** directly derived from the propargylation reaction.

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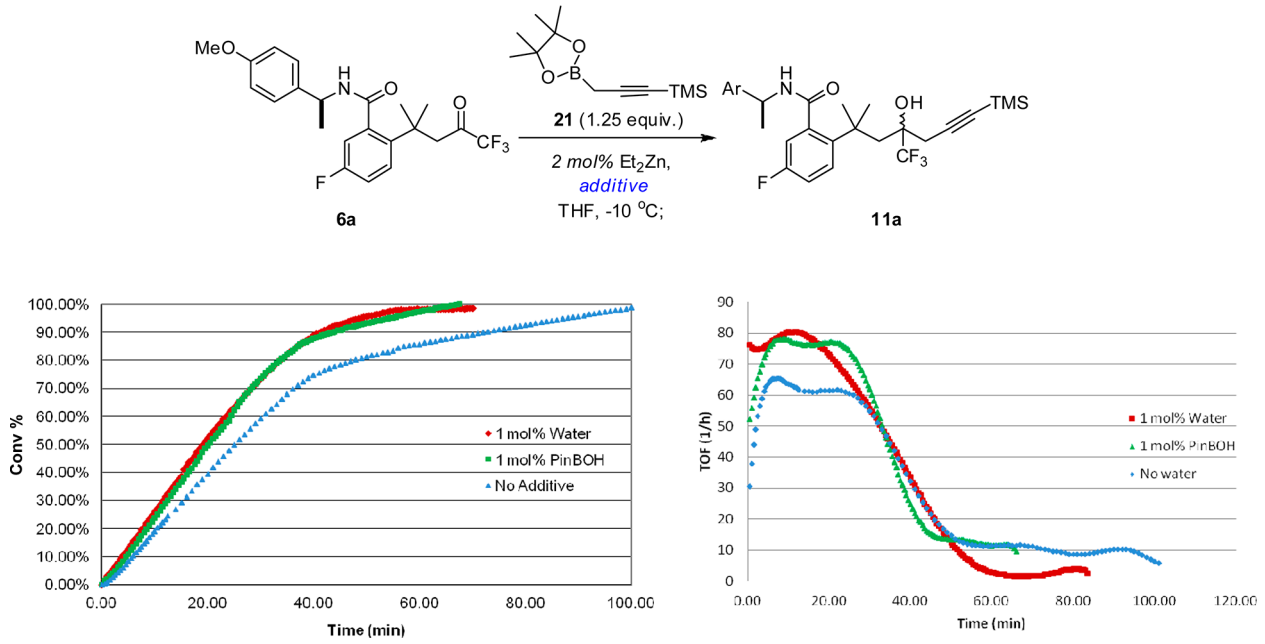

Figure 7. Additive effect on the zinc-catalyzed propargylation of ketone **6a**. Reaction performed by charging diethyl zinc to a solution of the ketone [**6a**] = 0.359 M and [**21**] = 0.449 M with the indicated additive in anhydrous THF at −10 °C. Reaction progress monitored by React IR. Turnover Frequency (TOF) was per hour.

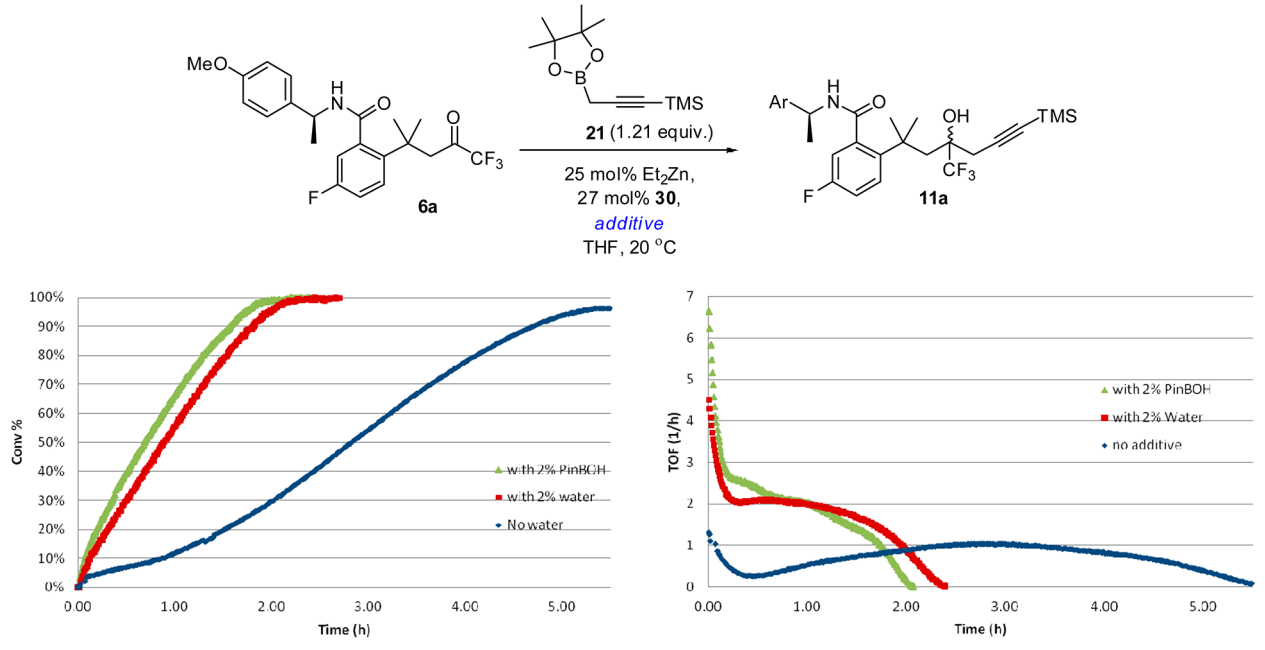

Figure 8. Additive effect on the zinc-catalyzed diastereoselective propargylation of ketone **6a**. Reaction performed by charging an aged (40 °C for 3 h) solution of diethyl zinc and ligand **30** in anhydrous THF to an anhydrous THF solution of the ketone [**6a**] = 0.285 M, borolane [**21**] = 0.346 M and the indicated additive in anhydrous THF at 20 °C. Reaction progress monitored by React IR. Turnover Frequency (TOF) was per hour.

In contrast to zinc-mediated asymmetric alkynyl, vinyl, aryl, alkyl, and propargyl additions to aldehydes and ketones catalyzed by chiral amino-alcohol ligands,[31] no asymmetric induction was observed with amino-alcohol ligands for the zinc-mediated asymmetric propargylation utilizing the propargyl borolane **21** reagent. Typical zinc-mediated asymmetric additions operate by ligand acceleration which effectively compete with the nonligated and nonselective pathway and proceed by a rapid Schlenk equilibration between the ligand, alkoxide product, and zinc salts.[31,63] Contrary to the classical zinc-mediated additions, catalytic diethyl zinc without a ligand promoted a rapid propargylation of carbonyl compounds with the propargyl borolane reagent **21**. Furthermore, the asymmetric propargylation utilizing an amino-acid ligand was shown to be ligand decelerating with a decrease in reaction rate of approximately 800% over the nonligated process *vide supra*. NMR analysis of the complex generated from diethyl zinc and *N*-iPr-L-Proline **30** showed clean consumption of diethyl zinc and formation of the *N*-iPr-L-Pro-Zn-Et complex **50** albeit with broad peaks indicative of aggregation[49] (Figure 10). Subjecting

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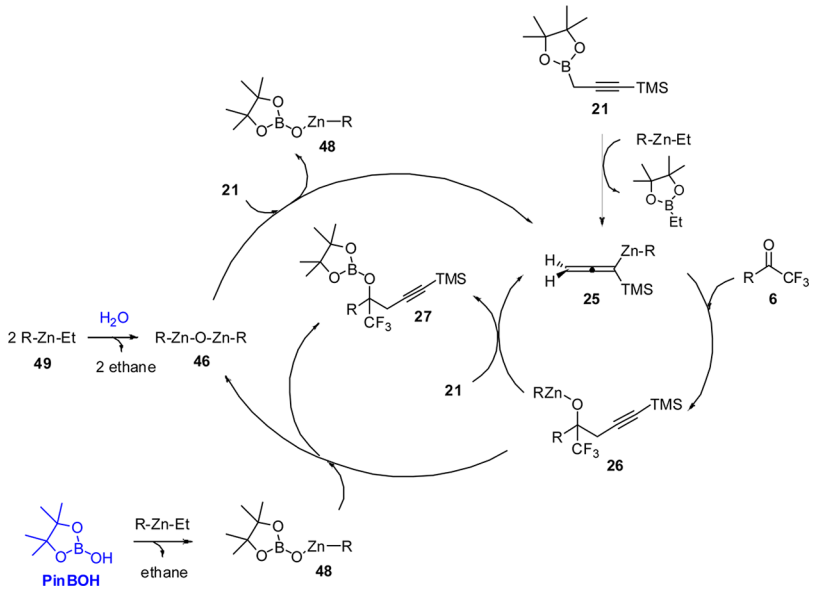
Scheme 3. Mechanistic Proposal for the Water Effect on the Zinc-catalyzed Propargylation



the same complexation conditions to a solution of diethyl zinc and a stoichiometric amino-alcohol ligand, *N*-Methyl ephedrine **13**, afforded a complex mixture in which the amino-alcohol zinc complex was not identifiable.[64] The effective zinc complexation with amino-acid ligands utilized in the zinc-catalyzed asymmetric propargylation achieved asymmetric induction by minimizing the amount of the nonligated zinc species which can competitively catalyze a nonselective background reaction. However, alternative mechanisms and competitive reactions are reasonably expected for zinc-catalyzed asymmetric propargylations based on different processes to generate an allenyl zinc intermediate such as demonstrated by the good asymmetric induction achieved by Trost et al. in an amino-alcohol-catalyzed and zinc-mediated asymmetric propargylation utilizing an iodopropyne or iodoallene reagent.[16]

CONCLUSION

A stereoselective zinc-catalyzed propargylation of trifluoromethyl ketones with a propargyl borolane and a chiral amino-acid ligand was developed. The process provided reasonable stereoselective induction for the propargylation of both aliphatic and aromatic trifluoromethyl ketones with use of a relatively inexpensive ligand and transition metal. Catalytic water was shown to accelerate the zinc-catalyzed propargylation with a pronounced effect on the stereoselective reaction with trifluoromethyl ketones. Based on the kinetically determined rate limiting boron−zinc exchange, a reasonable rationalization for the influence of catalytic water on the zinc-catalyzed propargylation relates to water generating an intermediate which can catalyze the key exchange. The proffered cocatalysis model enabled the prediction of pinacol boronic acid as an equivalent additive to water which provided a nearly identical reaction rate acceleration and profile as water. Furthermore, a facile closed six member inversion transition state for the B/Zn exchange with a propargyl borolane reagent was formulated based on an exchange initiating Lewis acid−base interaction between the propargyl borolane reagent and a zinc alkoxide ligand. Overall, these developments enabled a zinc-catalyzed asymmetric propargylation with an amino-acid ligand to be developed and provided for an operationally simple and cost-effective process to prepare pharmaceutically valuable chiral homopropargylic trifluoromethyl alcohols.

EXPERIMENTAL SECTION

All reactions were conducted under a dry nitrogen or argon atmosphere unless otherwise noted. Enantiomeric[45] and diastereomeric ratios were determined by high performance liquid chromatography (HPLC) with the noted conditions and analytical columns. Water content was determined by Karl Fischer titration. NMR analysis was performed on a 400 or 500 MHz instrument. Carbon NMR spectroscopy was conducted with proton decoupling. Chemical shifts (δ) are reported in ppm from tetramethylsilane (TMS, 0 ppm) and calibrated to TMS or to the residual solvent resonances (1H: $CDCl_3$ 7.26 ppm, CD_3OD 3.30, DMSO-d_6 2.49; 13C: $CDCl_3$ 77.0, CD_3OD 49.0, DMSO-d_6 39.5). NMR spectral data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant, and number of protons. High resolution mass spectroscopy was performed on a TOF instrument with ESI and positive or negative ionization as indicated. Propargyl Borolane **21** was prepared by our published procedure.[35b] Ligands **17**,[65] **18**,[66] **19**,[65b,67] **28**,[68] **29**,[69] **32**,[70] **34**,[71] **35**,[72] and **36**[73] were prepared according to known procedures. Trifluoromethyl ketones **6a**,[6] **6b**,[3b,25d] **6c**,[3b] **6d**,[6,8a] **6e**,[3b] **6f**,[25d] and **6j**[74] were prepared according to published procedures. Trifluoromethyl ketones **6g**, **6h**, and **6i** were obtained from commercial suppliers and utilized as received. Reagent grade solvents were utilized unless otherwise specified. All other reagents were utilized as received without further purification. Isothermal reactions were performed in a reactor system wherein the internal temperature was automatically controlled by adjustment of the jacket temperature. Reaction monitoring by React IR was performed by Fourier transform infrared spectroscopy (FTIR) utilizing a silver halide 9.5 mm × 1.5 m fiber probe interface.

***N*-Me-L-Pro (16).** L-Proline (6.0 g, 52 mmol), formaldehyde (37% in water, 6.2 mL, 83 mmol) methanol (70 mL) and 10 wt % Pd/C (1.50 g, 1.41 mmol) were charged to a pressure reactor. The reactor was flushed with argon followed by hydrogen. The vessel was pressurized with hydrogen to 200 psi and agitated at 50 °C for 2 d. The reaction was cooled to 20 °C and flushed with nitrogen. The reaction was diluted with methanol (50 mL) and filtered through a Celite (10 g) plug eluting with methanol (50 mL). The filtrate was concentrated *in vacuo* to an oil. The oil was azeotropically dried by distillation at 1 atm in toluene with a Dean−Stark trap. The resulting mixture was cooled to ambient temperature and concentrated *in vacuo* to a solid. The solid was dissolved in *n*-propanol (17 mL) at 90 °C.

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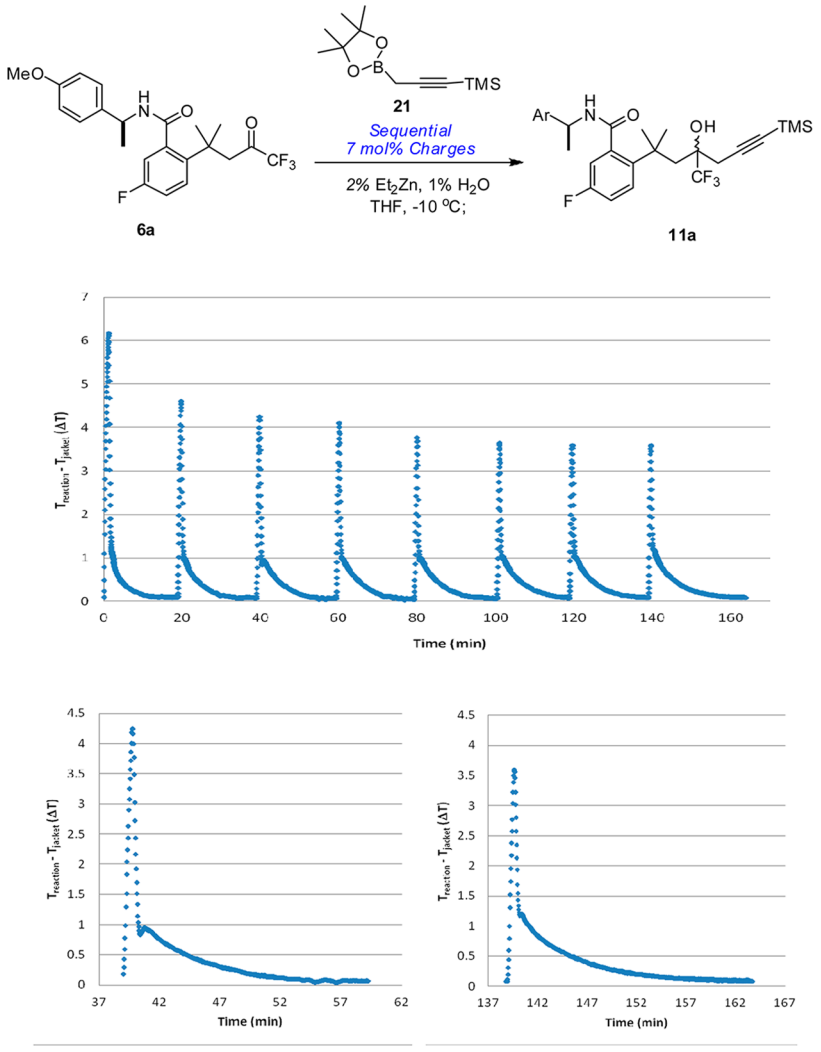

Figure 9. Calorimetric reaction profile for the propargylation of ketone **6a** with sequential additions of the propargyl borolane **21**. Reaction performed by the sequential addition, at the indicated time interval, of 7 mol % borolane **21** to trifluoromethyl ketone **6a** [0.55 M] with 2 mol % diethyl zinc and 1 mol % water in anhydrous THF at 20 °C under isothermal conditions. Calorimetry and reaction rate correlation under the relationship that $T_{reaction} - T_{jacket} = \Delta T$, $\Delta T \; \alpha$ q, and q α d[**11a**]/dt.[48]

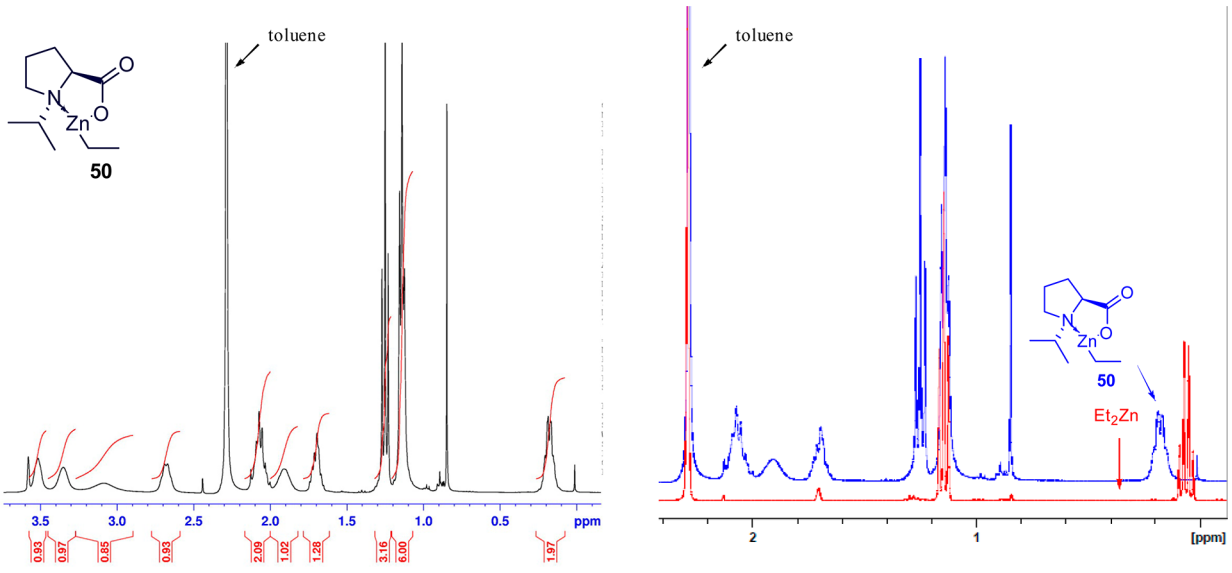

Figure 10. ^{1}H NMR analysis of complex **50**. ^{1}H NMR in THF-d^8 400 MHz at 20 °C.

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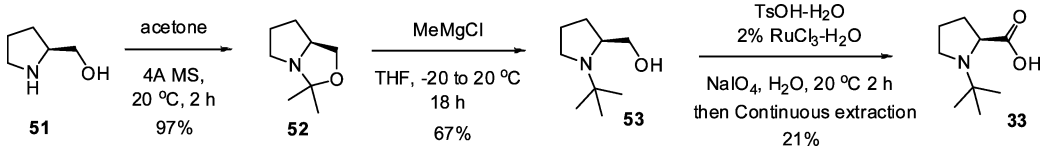
Scheme 4. Preparation of *N*-*t*-Bu-L-Pro 33



The homogeneous solution was diluted at 90 °C with toluene (100 mL). The solution was cooled to 50 °C; at which point, the solution was seeded to induce crystallization. The mixture was gently agitated and allowed to cool to 20 °C over 45 min. The mixture was diluted with MTBE (60 mL) dropwise over 30 min. The mixture was agitated for an addition hour. The solids were collected by filtration, washed with MTBE, and dried in a vacuum oven with a nitrogen stream at 70 °C for 14 h to afford *N*-Me-L-Pro **16** as an off white solid (4.38 g, 65%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 3.47−3.34 (m, 2H), 2.86−2.77 (m, 1H), 2.67 (s, 3H), 2.23−2.11 (m, 1H), 1.95−1.82 (m, 2H), 1.78−1.63 (m, 1H). **^{13}C NMR** (100 MHz, DMSO-d^6) δ 169.1, 69.9, 55.4, 40.4, 28.7, 23.1. $[\alpha]_D$ = −80 (*c* = 1.12 in MeOH). (Lit.[75] $[\alpha]_D$ = −78, *c* = 1.5 in MeOH). **HRMS-ESI** $C_6H_{11}NO_2$ calcd for $[M + H]^+$ 130.0863 found 130.0858.

***N,N*-Dimethyl-L-tert-Leucine (20).** A mixture of L-*tert*-Leucine (2.37 g, 18.1 mmol), aqueous formaldehyde (37 wt %, 2.96 mL, 40 mmol), Pd on carbon (10 wt % wet, 1.0 g) in methanol (4 mL) was agitated under a 200 psi hydrogen atmosphere at 55 °C for 72 h. The reaction was cooled to ambient temperature, flushed with nitrogen and filtered through a Celite plug with a methanol rinse. The filtrate was concentrated *in vacuo* to an oil and azeotropically dried by distillation with toluene at 1 atm with a Dean−Stark trap. The resulting heterogeneous mixture was concentrated to a solid. The solid was recrystallized with MeOH and MTBE to provide the ligand **20** as a which solid (2.18g, 76%). **^{1}H NMR** (400 MHz, MeOH-d_4) δ 3.31 (s, 1H), 2.98 (s, 6H), 1.21 (s, 9H). **^{13}C NMR** (100 MHz, MeOH-d^4) δ 172.03, 81.38, 44.42, 33.82, 28.77. $[\alpha]_D$ = +23 (*c* = 0.55 in MeOH). **HRMS-ESI** $C_8H_{17}NO_2$ calcd for $[M + H]^+$ 160.1332 found 160.1328.

***N*-Isopropyl-L-Proline (30).** Ligand **30** was prepared by modified published procedures.[69,70a] L-Proline (28 g, 240 mmol), 10 wt % Pd on Carbon (7.8 g, 7.3 mmol) acetone (89 mL) and methanol (250 mL) were charged to a pressure reactor. The reactor was flushed with nitrogen followed by hydrogen. The vessel was pressurized with hydrogen to 200 psi and agitated at 80 °C for 2 d. The reaction was cooled to 20 °C and flushed with nitrogen. The reaction mixture was diluted with methanol (200 mL) and filtered through a Celite (30 g) plug eluting with methanol (100 mL). The filtrate was concentrated *in vacuo* to a yellow oil and chased with toluene. Concentration *in vacuo* provided a solid. The solid was suspended in toluene (70 mL), and the solids were dissolved at 90 °C by the addition of *n*-propanol (70 mL). The resulting solution was further diluted with toluene (250 mL) at 90 °C. The homogeneous solution was slowly cooled to 20 °C over 1 h to induce crystallization. The mixture was diluted with MTBE (650 mL) dropwise over 30 min at 20 °C. After agitating the slurry for 1 h, the solids were collected by filtration and washed with MTBE to provide *N*-iPr-L-Pro **30** as a slightly off white crystalline solid (35.6 g, 93%) after drying in a vacuum oven at 70 °C with a nitrogen stream for 14 h. **Chiral HPLC** with a Chirobiotic T (4.6 × 150 mm) column (200 nm detection, 5% MeCN in HPLC grade water, 2.5 mL/min, 50 °C) showed >99% ee favoring the 1.6 min over the 2.2 min peak. **^{1}H NMR** (400 MHz, MeOH-d_4) δ 3.93 (dd, *J* = 4.4, 9.3 Hz, 1H), 3.70 (ddd, *J* = 2.9, 6.9, 10.8 Hz, 1H), 3.57 (septet, *J* = 6.5, Hz, 1H), 3.16 (ddd, *J* = 6.8, 10.6, 10.6 Hz, 1H), 2.40−2.25 (m, 1H), 2.20−2.10 (m, 1H), 2.08−1.98 (m, 1H), 1.93−1.75 (m, 1H), 1.32 (d, *J* = 6.6 Hz, 3H), 1.33 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, MeOH-d_4) δ 173.9, 67.4, 57.9, 53.2, 31.0, 25.0, 18.4. $[\alpha]_D$ = −55 (*c* = 1.28 in MeOH). **HRMS-ESI** $C_8H_{15}NO_2$ calcd for $[M + H]^+$ 158.1176 found 158.1171.

***N*-Cyclopentyl-L-Proline (31).** A mixture of proline (10.1 g, 87.7 mmol), cyclopentanone (37 g, 0.44), and Pd on Carbon (10 wt %, 1 g) were agitated in methanol (174 mL) under hydrogen (50 psi) at 50−80 °C for 16 h. After cooling to ambient temperature and flushing with nitrogen, the solids were removed by filtration. The filtrate was concentrated *in vacuo* and dried to a solid. The solid was recrystallized from *n*-propanol, toluene and MTBE to afford the desired product **31** (13 g, 81%) as an off white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 3.65−3.55 (m, 2H), 3.55−3.46 (m, 1H), 2.89 (ddd, *J* = 6.2, 10.5, 10.5 Hz, 1H), 2.20−2.05 (m, 1H), 2.05−1.95 (m, 1H), 1.92−1.80 (m, 3H), 1.80−1.55 (m, 5H), 1.55−1.40 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 169.6, 67.6, 65.3, 53.4, 29.4, 28.51, 28.46, 23.7, 23.5, 23.4. $[\alpha]_D$ = −54 (*c* = 0.52 in MeOH). **HRMS-ESI** $C_{10}H_{17}NO_2$ calcd for $[M + H]^+$ 184.1332 found 184.1328.

***N*-*t* -Butyl-L-Pro (33).** (Scheme 4): A mixture of (S)-prolinol **51** (20.5 g, 203 mmol), 4A MS (20 g) in acetone (150 mL) was agitated under argon at 20 °C for 2 h; at which point, GC analysis showed complete conversion. The reaction mixture was filtered through a Celite plug eluting with MTBE. The filtrate was concentrated *in vacuo* to provide (*S*)-3,3-dimethylhexahydropyrrolo[1,2-c]oxazole **52** as a yellow homogeneous oil (27.7g, 97%) which was used in the next operation without further purification. **^{1}H NMR** (500 MHz, C_6D_6) δ 3.73 (t, *J* = 7.7 Hz, 1H), 3.66−3.59 (m, 1H), 3.20 (dd, *J* = 6.6, 6.6 Hz, 1H), 2.66 (dd, *J* = 7.2, 7.2 Hz, 1H), 2.55−2.47 (m, 1H), 1.84−1.75 (m, 1H), 1.70−1.51 (m, 2H), 1.41 (s, 3H), 1.32 (s, 3H), 1.24−1.14 (m, 1H). Intermediate **52** (5.0 g, 35 mmol) was charged neat to a solution of methyl magnesium chloride (3.0 M in THF, 29.5 mL, 88.5 mmol) in anhydrous THF (120 mL) at −20 °C under argon. The resulting solution was agitated at 18−20 °C for 18 h. The reaction was quenched by the addition of 3 M HCl (60 mL). Sodium potassium tartrate tetrahydrate (22.5 g, 79.7 mmol) was charged to the reaction mixture as a solid, and the reaction mixture was agitated at ambient temperature for 2 h. Aqueous NaOH (3 M, 16 mL, 48 mmol) was charged to the reaction, and the mixture was agitated at ambient temperature for 18 h. The reaction was extracted with ethyl acetate (6 × 50 mL). The aqueous portion contained significant amount of the product. The aqueous portion was treated with aqueous NaOH (3M, 50 mL) followed by brine (10 mL) and extracted with methylene chloride (6 × 50 mL). The combined organic portions were dried with Na_2SO_4, filtered and concentrated *in vacuo* to provide (*S*)-(1-tert-butylpyrrolidin-2-yl)methanol **53** as an oil in approximately 80 wt % purity (4.66 g, 80 wt %, 67%) which was used in the next operation without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.42 (dd, *J* = 5.9, 9.8 Hz, 1H), 3.27 (dd, *J* = 3.4, 10.3 Hz, 1H), 3.20−3.14 (m, 1H), 3.0−2.9 (m, 1H), 2.77−2.70 (m, 1H), 1.82−1.64 (m, 5H), 1.09 (s, 9H). *p*-Toluenesulfonic acid monohydrate (8.8 g, 46 mmol) was charged to a suspension of alcohol **53** (7.59 g, ∼80 wt %, 38.6 mmol) in water (130 mL). After agitation until a homogeneous solution was obtained, $RuCl_3$ Hydrate (174 mg, 0.84 mmol) followed by $NaIO_4$ (24.8 g, 116 mmol) were charged to the reaction. The reaction was agitated at ambient temperature for 1.5 h; at which point, LC-MS showed >95% oxidation to the carboxylic acid product. The reaction was slowly quenched by the portion wise addition of sodium sulfite (68.5 g) at a rate to control the batch temperature at 20−40 °C until no exothermic reaction was observed upon addition of additional sodium sulfite. The reaction mixture was filtered. The pH of the aqueous filtrate was adjusted to 7.5 by the addition of aqueous NaOH (40 wt % in water). This aqueous portion was subjected to a continuous extraction by distillation with methylene chloride for 5 d. The extracted organic portion was concentrated to a solid. The solids were suspended in methanol (100 mL) and polished filtered through a Celite plug. The filtrate was concentrated *in vacuo* to a solid and chased with toluene. The solid was recrystallized in a solvent system of *n*-propanol, toluene and MTBE to provide *N*-*t*-Bu-L-Pro **33** as an off-white solid (1.4 g, 21%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 3.86 (d, *J*

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= 9.8 Hz, 1H), 3.52 (dd, J = 6.4, 11.8 Hz, 1H), 3.08 (ddd, J = 6.4, 11.5, 11.5 Hz, 1H), 2.15−2.07 (m, 1H), 1.96−1.80 (m, 2H), 1.60−1.46 (m, 1H), 1.26 (s, 9H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 169.5, 64.1, 59.8, 48.8, 29.7, 24.6, 24.0. $[\alpha]_D$ = −50 (c = 0.50 in MeOH). **HRMS-ESI** $C_9H_{17}NO_2$ calcd for $[M + H]^+$ 172.1332 found 172.1332

(*S*)-2-(1-Isopropylpyrrolidin-2-yl)propan-2-ol (37). (S)-2-(pyrrolidin-2-yl)propan-2-ol[76] (1.95 g, 15.1 mmol) was subjected to a heterogeneous reaction with 10 wt % Pd on carbon (300 mg) in acetone (14.2 mL) and methanol (22 mL) under hydrogen (40 psi) at room temperature for 6 h. The reaction mixture was filtered, and the filtrate was concentrated to an oil. Purification by alumina chromatography (ethyl acetate in hexanes) provided the intended amino alcohol **37** as a nearly colorless oil (1.3 g, 50%). **^{1}H NMR** (400 MHz, CD_3OD) δ 3.14 (septet, J = 6.6 Hz, 1H), 2.82−2.71 (m, 3H), 1.80−1.58 (m, 4H), 1.14 (s, 3H), 1.12 (d, J = 6.9 Hz, 3H), 1.11 (s, 3H), 0.95 (d, J = 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, CD_3OD) δ 74.53, 71.01, 53.93, 46.81, 28.78, 27.71, 26.68, 26.10, 23.00, 14.59. $[\alpha]_D$ = −39 (c = 0.57 in MeOH). **HRMS-ESI** $C_{10}H_{21}NO$ calcd for $[M + H]^+$ 172.1696 found 172.1702.

(*S*)-(1-Isopropylpyrrolidin-2-yl)diphenylmethanol (38). (S)-diphenyl(pyrrolidin-2-yl)methanol[77] (12.0 g, 47.3 mmol) was subjected to a reaction with acetone (13.8, 237 mmol), sodium cyanoborohydride (6.0 g, 95 mmol) in acetonitirle (100 mL) and acetic acid (0.1 mL) at ambient temperature for 18 h. The reaction was concentrated to an oily solid. The residue was dissolved in ethylacetate and water. The layers were separated. The organic layer was diluted with brine and subjected to a thorough back extraction with ethyl acetate. The organic layers were concentrated to a solid. Purification by silica gel chromatography (ethyl acetate in hexanes) provided the intended amino alcohol **38** as a which solid (3.5 g, 25%). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.65−7.60 (m, 2H), 7.58−7.53 (m, 2H), 7.28−7.19 (m, 4H), 7.15−7.08 (m, 2H), 4.11 (dd, J = 4.6, 8.8 Hz, 1H), 2.90−2.83 (m, 1H), 2.82−2.74 (m, 1H), 2.08 (septet, J = 6.8, 1H), 1.89−1.76 (m, 1H), 1.70−1.51 (m, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, CD_3OD) δ 149.95, 148.10, 128.82, 128.81, 127.15, 127.13, 127.00, 126.62, 78.93, 68.98, 50.69, 46.44, 31.06, 25.85, 22.95, 13.60. $[\alpha]_D$ = −6.9 (c = 0.73 in MeOH). **HRMS-ESI** $C_{20}H_{25}NO$ calcd for $[M + H]^+$ 296.2009 found 296.2015.

GENERAL PROCEDURE FOR THE ZINC MEDIATED ASYMMETRIC PROPARGYLATION

5-Fluoro-2-((*S*)-4-hydroxy-2-methyl-4-(trifluoromethyl)hept-6-yn-2-yl)-*N*-((*S*)-1-(4-methoxy-phenyl)ethyl)benzamide (7a). *N*-iPr-L-Pro **30** (5.993 kg, 98.7 wt %, 37.63 mol) was charged to a dried 200 L reactor under nitrogen followed by THF (KF < 500 ppm, 76.7 kg). After obtaining adequate agitation at 20 °C, diethyl zinc[78] (2.30 M in toluene, d = 0.941 g/mL, 14.95 kg, 36.5 mol) was charged to the slurry subsurface at a rate to maintain the batch temperature between 20 to 35 °C. The heterogeneous slurry with a gentle gas evolution was agitated at 40 to 45 °C for 3 h to afford a homogeneous solution with no gas evolution. The batch was cooled to 20 °C. [Note: Additional water was not charged to the batch since an unknown and adequate amount of water introduced from the ketone **6a**, borolane **21**, and solvent THF at the next addition was sufficient for good conversion and diastereoselectivity. For reproducibility, 22 g of water as a THF (100−200 mL) solution is recommended to be charged to the batch at this point for reasons detailed in this manuscript.] A solution of trifluoromethyl ketone **6a** (13.29 kg, 97.8 wt %, 30.6 mol) and propargyl borolane **21** (9.36 kg, 93.5 wt %, 36.7 mol) in THF (<500 ppm water, 23.1 kg) prepared under nitrogen was charged to the reactor slowly over 10 h at 20 °C. After agitation for an additional 3 h, HPLC analysis (TSKgel SuperODS, 4.6 mm × 5 cm, 10 to 90% gradient of MeCN in water over 8 min) showed 99% conversion and 81:19 diastereoselectivity for the homopropargylic alcohol **11a** intermediate. The reaction was quenched by the exothermic slow addition of aqueous HCl (3.0 M, 38.5 kg) at a rate such that the gas evolution was controlled and the batch temperature was maintained between 20 to 35 °C. The resulting mixture was agitated for an additional 1 h; at which point, the layers were separated. A methanolic sodium methoxide solution (25 wt % NaOMe, 16.77 kg, 77.6 mol) was charged to the well agitated batch at 20 to 35 °C. The batched was aged for an additional 90 min at 30 to 35 °C; at which point, >99% deprotection was observed by HPLC *vide infra*. After cooling the batch to 20 °C, aqueous HCl (3.0 M, 23.14 kg) was charged to the reactor at a rate to maintain the batch temperature between 20 to 35 °C. Water (47.71 kg) was subsequently charged to the batch. For an effective workup, the pH of the aqueous layer should be 5.0 to 7.0 and adjusted if necessary. The pH of the aqueous layer for this batch was 6.9. The contents of the batch were distilled under vacuum with a batch temperature of no more than 65 °C to remove 117.4 kg of distillate and afforded an aqueous slurry. Isopropyl acetate (90.61 kg) was charged to the batch at 60 °C, and the batch temperature was subsequently adjusted to 20 °C. Aqueous HCl (3.0 M, 5.46 kg) was charged to the batch. The batch was agitated for one hour; at which point, the layers were separated. The organic portion was washed with water (26.0 kg). The organic portion was concentrated under vacuum with a batch temperature of no more than 75 °C to remove 75.3 kg of distillate. The batch temperature was adjusted to 80 to 83 °C and held at this temperature for 30 min to dissolve the solids. The batch temperature was adjusted to 75 °C; at which point, a slurry of seeds (33 g) in a solvent mixture of isopropyl acetate (91 g) and heptane (221 g) was charged to the batch to induce crystallization. The batch was cooled to 60 °C and aged at this temperature for 30 min followed by cooling to 20 °C over one hour. Heptane (10.70 kg) followed by isopropyl acetate (4.72 kg) were charged to the batch consecutively over 90 min. Additional heptane (46.3 kg) was charged to the batch over 90 min. After aging the batch at 20 °C for 10 h, the product was isolated by filtration. The solids were washed with 15 vol% isopropyl acetate in heptane and dried in a vacuum oven at no higher than 55 °C with a nitrogen stream until by thermogravimetric analysis (TGA) < 1 wt % loss up to 140 °C was observed. The homopropargylic alcohol **7a** was isolated as a white to off white solid (10.795 kg, 98.5 wt %, 75%) in 99.2:0.8 dr and 99:1 site selectivity favoring the homopropargylic alcohol **7a** over the allenylic alcohol **23**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 5.1, 8.7 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.05 (ddd, J = 3.1, 8.5, 8.5 Hz, 1H), 6.92 (d, J = 8.5 Hz, 2H), 6.84 (dd, J = 3.4, 8.7 Hz, 1H), 6.10 (d, J = 8.3 Hz, 1H), 6.05 (s, 1H), 5.29 (dddd, J = 7.1, 7.1, 7.1, 7.1 Hz, 1H), 3.82 (s, 3H), 2.56 (d, J = 15.3 Hz, 1H), 2.51 (d, J = 18.5 Hz, 1H), 2.40 (d, J = 17.8 Hz, 1H), 2.29 (d, J = 15.3 Hz, 1H), 2.07 (t, J = 2.1 Hz, 1H), 1.62 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H), 1.42 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.8 (d, J = 1.8 Hz), 160.5 (d, J = 249 Hz), 159.3, 140.5 (d, J = 3.5 Hz), 137.3 (d, J = 5.8 Hz), 133.9, 130.1 (d, J = 7.6 Hz), 127.5, 125.7 (q, J = 289 Hz), 116.5 (d, J = 19.4 Hz), 115.4 (d, J = 22.6 Hz), 114.3, 78.8, 75.4 (q, J = 26.7 Hz), 71.7, 55.3, 49.1, 42.8, 37.0, 33.3, 33.2, 23.9, 20.64. **HRMS-ESI** $C_{25}H_{27}F_4NO_3$ calcd for $[M + H]^+$ 466.1998 found 466.1987.

GENERAL PROCEDURE FOR THE ZINC CATALYZED ASYMMETRIC PROPARGYLATION

5-Fluoro-2-((*R*)-4-hydroxy-2-methyl-4-(trifluoromethyl)-7-(trimethylsilyl)hept-6-yn-2-yl)-*N*-((*S*)-1-(4-methoxyphenyl)-ethyl)benzamide (11a). Diethyl zinc[78] (2.3 M in toluene, 326 μL, 0.75 mmol) was charged to an anhydrous suspension of *N*-isopropyl-L-proline **30** (127 mg, 0.81 mmol) in THF (2.1 mL) under argon at ambient temperature. The reaction slurry with a gentle gas evolution was agitated at 40 °C for 3 h; at which point, no gas evolution was observed and a homogeneous solution of the *N*-iPr-L-Pro-Zn-Et **50** was obtained. The solution was cooled to ambient temperature; at which point, a water-THF solution (0.26 wt % water in THF, 416 mg, 0.06 mmol water) was charged to the catalyst solution. The solution was agitated for 30 min. The homogeneous solution was cooled to −40 °C. An anhydrous homogeneous solution of ketone **6a** (1.25 g, 97.9 wt %, 2.9 mmol) and borolane **21** (855 mg, 3.6 mmol) in THF (3.5 mL) held at ambient temperature was charged to the catalyst solution at −40 °C dropwise over 6 h. The reaction was agitated at −40 °C for 2 d; at which point, complete conversion, 90:10 dr favoring the 7.76 over the 7.66 min diastereomer determined by HPLC (TSKgel SuperODS, 4.6 mm × 5 cm, 10 to 90% gradient of

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MeCN in water over 8 min), and 93:7 site selectivity favoring propargylation over allenylation were observed. The reaction was quenched by the addition of 3 M aqueous HCl (1 mL) and allowed to warm to ambient temperature. Diethanolamine (1.5 mL) was charged to the reaction, and the reaction was agitated for 2 h. The reaction was diluted with isopropyl acetate (40 mL) and washed with water (2 × 20 mL). The organic portion was concentrated to an oil. Purification by silica gel chromatography (ethyl acetate and hexanes) provided homopropargylic alcohol **11a** as an inseparable diastereomeric mixture of 90:10 dr favoring the desired diastereomer **11a** (1.25 g, 78%). **Major Diastereomer**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (dd, J = 5.6, 9.0 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.04 (ddd, J = 2.5, 7.9, 7.9 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 6.82 (dd, J = 2.9, 8.4 Hz, 1H), 6.10 (d, J = 8.8 Hz, 1H), 6.02 (s, 1H), 5.28 (dddd, J = 7.1, 7.1, 7.1, 7.1 Hz, 1H), 3.82 (s, 3H), 2.54 (d, J = 15.2 Hz, 1H), 2.51 (d, J = 17.9 Hz, 1H), 2.40 (d, J = 17.9 Hz, 1H), 2.29 (d, J = 15.2 Hz, 1H), 1.63 (s, 3H), 1.59 (d, J = 7.1 Hz, 3H), 1.42 (s, 3H), 0.16 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.8 (d, J = 1.7 Hz), 160.5 (d, J = 248 Hz), 159.2, 140.6 (d, J = 3.85 Hz), 137.3 (d, J = 5.7 Hz), 133.9, 130.1 (d, J = 7.5 Hz), 127.5, 125.8 (q, J = 291 Hz), 116.5 (d, J = 19.4 Hz), 115.4 (d, J = 22.9 Hz), 114.3, 101.4, 88.6, 75.6 (q, J = 25.9 Hz), 55.3, 49.0, 42.7, 36.9, 33.35, 33.28, 25.1, 20.6, −0.17. **Minor Diastereomer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (dd, J = 5.4, 9.6 Hz, 1H), 7.33−7.27 (m, 2H), 7.04 (ddd, J = 3.0, 7.7, 7.7 Hz, 1H), 6.99−6.87 (m, 2H), 6.82 (dd, J = 2.9, 8.9 Hz, 1H), 6.07 (d, J = 8.3 Hz, 1H), 5.96 (s, 1H), 5.27 (dddd, J = 7.1, 7.1, 7.1, 7.1 Hz, 1H), 3.81 (s, 3H), 2.52 (d, J = 15.4 Hz, 1H), 2.43 (d, J = 17.5 Hz, 1H), 2.41 (d, J = 17.5 Hz, 1H), 2.23 (d, J = 15.1 Hz, 1H), 1.62 (d, J = 7.2 Hz, 3H), 1.60 (s, 3H), 1.18 (s, 3H), 0.15 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.8 (d, J = 1.7 Hz), 160.5 (d, J = 248 Hz), 159.2, 140.7 (d, J = 3.85 Hz), 137.4 (d, J = 5.7 Hz), 133.5, 130.1 (d, J = 7.5 Hz), 127.7, 125.8 (q, J = 291 Hz), 116.4 (d, J = 19.4 Hz), 115.5 (d, J = 22.9 Hz), 114.2, 101.3, 88.6, 75.7 (q, J = 25.9 Hz), 55.3, 49.2,42.7, 36.8, 33.21, 33.16, 25.2, 20.9, −0.18. **HRMS-ESI** for diastereomeric mixture $C_{28}H_{35}F_4NO_3Si$ calcd for $[M + H]^+$ 538.2395 found 538.2383.

Allene Isomer 23. Diethyl zinc (1.1 M in toluene, 64 μL, 70 μmol) was charged to a solution of ketone **6a** (600 mg, 1.41 mmol) and allenyl borolane **22** (328 mg, 1.97 mmol) in toluene (10 mL) under argon at ambient temperature. The homogeneous reaction was agitated for 3 h; at which point, HPLC showed complete conversion. Diethanolamine (1 g) was charged to the reaction, and the reaction was agitated at ambient temperature for 45 min. The reaction was diluted with isopropyl acetate (20 mL) and washed with aqueous HCl (1.5 M, 2 × 30 mL) followed by water (2 × 30 mL). The organic portion was concentrated to an oil. ^{1}H NMR analysis on the oil showed 95:5 site selectivity favoring allenylation over propargylation. The product was purified by silica gel chromatography (12% EtOAc in hexanes) to provide the intended allenyl alcohol **23** as a nearly equal mixture of diastereomers and as a white foam (575 mg, 88% yield). **Mixture of Diastereomers: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39−7.32 (m, 1H), 7.32−7.25 (m, 2H), 7.02−6.95 (m, 1H), 6.92−6.79 (m, 3 H), 6.37 (t, J = 7.0 Hz, 0.5H), 6.27 (t, J = 6.0 Hz, 0.5 H), 5.41 (bs, 0.5H), 5.30−5.18 (m, 1H), 5.16−5.08 (m, 1H), 5.05 (bs, 0.5 H), 4.89−4.80 (m, 1H), 4.73−4.64 (m, 1H), 3.79 (s, 1.5 H), 3.78 (s, 1.5 H), 2.61 (d, J = 15.6 Hz, 0.5 H), 2.57 (d, J = 15.6 Hz, 0.5 H), 2.06 (d, J = 15.6 Hz, 0.5 H), 2.03 (d, J = 15.6 Hz, 0.5 H), 1.61−1.50 (m, 6H), 1.37 (s, 1.5 H), 1.22 (s, 1.5 H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.33, 207.07, 171.43 (d, J = 1.7 Hz), 171.30 (d, J = 1.7 Hz), 160.42 (d, J = 248 Hz), 160.40 (d, J = 248 Hz), 159.08, 159.04, 140.22 (d, J = 4.0 Hz), 140.02 (d, J = 3.6 Hz), 137.83 (d, J = 5.9 Hz), 137.53 (d, J = 5.7 Hz), 134.02, 133.97, 130.51 (d, J = 7.4 Hz), 130.38 (d, J = 7.4 Hz), 127.55, 127.48, 125.16 (q, J = 287 Hz), 125.10 (q, J = 287 Hz), 115.59 (d, J = 19.6 Hz), 115.43 (d, J = 19.6 Hz), 115.25 (d, 22.6 Hz), 115.17 (d, J = 22.6 Hz), 114.13, 114.05, 90.94, 90.84, 79.86, 79.45, 74.20 (q, J = 27.2 Hz), 55.23, 55.21, 49.00, 48.89, 44.87, 44.62, 37.13, 37.10, 32.70, 32.70, 32.11, 31.98, 20.90, 20.57. **HRMS-ESI** $C_{25}H_{27}F_4NO_3$ calcd for $[M + H]^+$ 466.1998 found 466.1996.

Allene Isomer 24. An analytical standard for the diastereomeric mixture of allene **24** was obtained after extensive purification by silica gel chromatography (EtOAc and hexanes) of the crude propargylation reaction mixture from the zinc-mediated diastereoselective propargylation of ketone **6a** and isolated as an amorphous white solid in less than 5% yield. **Mixture of Diastereomers: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40−7.33 (m, 1H), 7.33−7.28 (m, 2H), 7.04−6.96 (m, 1H), 6.94−6.81 (m, 3H), 6.12−6.03 (m, 1H), 5.36−5.22 (m, 2H), 4.56−4.43 (m, 2H), 3.81 (s, 1.66 H), 3.80 (s, 1.39 H), 2.70 (d, J = 15.9 Hz, 0.62 H), 2.58 (d, J = 15.2 Hz, 0.43 H), 2.25 (d, J = 15.1 Hz, 0.62 H), 2.17 (d, J = 15.2 Hz, 0.44 H), 1.64−1.58 (m, 3H), 1.50 (s, 1.2 H), 1.49 (s, 1.8 H), 1.34 (s, 1.8 H), 1.16 (s, 1.2 H), 0.05 (s, 3.4 H), 0.03 (s, 5.6 H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 210.01, 209.89, 171.58 (d, J = 1.8 Hz), 171.54 (d, J = 1.8 Hz), 160.26 (d, J = 248 Hz), 160.25 (d, J = 248 Hz), 159.19, 159.19, 141.53 (d, J = 3.8 Hz), 141.45 (d, J = 3.8 Hz), 137.20 (d, J = 5.8 Hz), 137.13 (d, J = 5.8 Hz), 134.05, 133.82, 130.35 (d, J = 7.4 Hz), 130.33 (d, J = 7.4 Hz), 127.73, 127.55, 126.02 (q, J = 288 Hz), 125.98 (q, J = 288 Hz), 116.10 (d, J = 19.9 Hz), 116.04 (d, J = 19.3 Hz), 115.26 (d, J = 22.5 Hz), 115.22 (d, J = 22.5 Hz), 114.23, 114.14, 98.02, 97.82, 77.93 (q, J = 26.4 Hz), 77.86 (q, J = 26.4 Hz), 71.72, 71.61, 55.30, 55.30, 49.10, 49.08, 45.57, 45.46, 37.69, 37.62, 34.50, 34.39, 31.43, 31.43, 20.77, 20.67, 0.47, 0.46. **HRMS-ESI** $C_{28}H_{35}F_4NO_3Si$ calcd for $[M + H]^+$ 538.2395 found 538.2390.

(*R*)-6-(5-Fluoro-2-methylphenyl)-6-methyl-4-(trifluoromethyl)-1-(trimethylsilyl)hept-1-yn-4-ol (11b). Homopropargylic alcohol (*S*)-**11b** was prepared by the general procedure for the zinc-catalyzed asymmetric propargylation with 1,1,1-trifluoro-4-(5-fluoro-2-methylphenyl)-4-methylpentan-2-one **6b** (0.787 g, 3.0 mmol) to provide alcohol (*S*)-**11b** as a colorless oil (1.01 g, 90%) in 90:10 enantiomeric ratio determined by chiralcel AD-H of the terminal alkyne derivative **7b** prepared by proto-desilylation with potassium carbonate in methanol (1% IPA in heptane, 2.0 mL/min, 210 nm) favoring the 3.26 min over the 2.97 min enantiomer. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (dd, J = 2.7, 12.1 Hz, 1H), 7.07 (dd, J = 7.0, 8.0 Hz, 1H), 6.83 (ddd, J = 2.9, 8.0, 8.0 Hz, 1H), 2.52 (s, 3H), 2.51 (d, J = 15.7 Hz, 1H), 2.46 (d, J = 18.9 Hz, 1H), 2.36 (s, 1H), 2.34 (d, J = 18.9 Hz, 1H), 2.27 (d, J = 15.7 Hz, 1H), 1.57 (s, 3H), 1.51 (s, 3H) 0.12 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.3 (d, J = 243.1 Hz), 147.2 (d, J = 6.1 Hz), 134.5 (d, J = 7.8 Hz), 131.6 (d, J = 3.0 Hz), 125.7 (q, J = 287.8 Hz), 114.6 (d, J = 22.7 Hz), 113.1 (d, J = 20.4 Hz), 99.5, 90.1, 75.1 (q, J = 26.4 Hz), 40.4, 38.6, 31.4, 30.7, 26.6 (q, J = 1.4 Hz), 22.7, −0.26. **HRMS-ESI** $C_{19}H_{26}F_4OSi$ calcd for $[M + NH_4]^+$ 392.2027 found 392.2020.

(*S*)-6-(5-Fluoro-2-methylphenyl)-6-methyl-4-(trifluoromethyl)hept-1-yn-4-ol (7b). *N*-iPr-L-Pro **30** (16.338 g, 97.6 wt %, 0.101 mol) was charged under nitrogen followed by THF (technical grade, 350 mL) to a reactor. After obtaining adequate agitation for the slurry at 22 °C, diethyl zinc[78] (2.30 M in toluene, d = 0.941 g/mL, 35.0 mL, 0.080 mol) was charged to the batch subsurface at a rate to maintain the batch temperature between 20 to 30 °C. The heterogeneous slurry with a gentle gas evolution was agitated at 40 to 45 °C for 45 min to afford a homogeneous solution. The batch was cooled to 20 °C and water (0.19 g, 0.01 mol) and THF (2 mL) were added. A solution of trifluoromethyl ketone **6b** (70 g, 0.267 mol) and propargyl borolane **21** (73.935 g, 86.0 wt %, 0.267 mol) in THF (206 mL) prepared under nitrogen was charged to the reactor slowly over 100 min at 20 °C. After rinsing the charge with THF (10 mL) and agitation for an additional 30 min, HPLC analysis showed 99% conversion. The reaction was quenched by the exothermic slow addition of aqueous HCl (3.0 M, 320 mL) at a rate such that the batch temperature was maintained between 20 to 25 °C. The resulting mixture was agitated for an additional 10 min; at which point, the layers were separated. A methanolic sodium methoxide solution (30 wt % NaOMe, 122.56 g, 0.681 mol) was charged to the well agitated batch at 20 to 35 °C followed by rinsing the charge with methanol (10 mL). The batched was agitated for an additional 40 min at 30 to 35 °C; at which point, >99% deprotection was observed by HPLC. After cooling the batch to 20 °C, aqueous HCl (3.0 M, 280 mL) was charged to the reactor at a rate to maintain the batch temperature between 20 to 30 °C. The resulting mixture was agitated for an additional 10 min; at which point, the layers were separated. The organic solution was concentrated under reduced pressure to the crude homopropargylic alcohol **7b** (94 g, 77.8 wt %, 91%). The desired

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product **7b** was isolated after purification by distillation *in vacuo* as a yellow oil (63.7 g, 89.9 wt %, 71%). Chiral HPLC with a Chiralpak AD-3 column (1.6% IPA in hexanes, 0.5 mL/min, 10 °C, 215 nm) showed 84.2:15.8 er favoring the 17.72 min peak over the 12.67 min peak. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.14 (dd, J = 2.6, 12.0 Hz, 1H), 7.08 (dd, J = 7.8, 8.1 Hz, 1H), 6.84 (ddd, J = 2.8, 8.0, 8.0 Hz, 1H), 2.53 (s, 3H), 2.51−2.43 (m, 2H), 2.37−2.29 (m, 2H), 2.27 (s, 1H), 2.08 (t, J = 2.5 Hz, 1H), 1.57 (s, 3H), 1.53 (s, 3H). **^{13}C NMR** (123 MHz, $CDCl_3$) δ 161.3 (d, J = 243 Hz), 147.0 (d, J = 6.1 Hz), 134.6 (d, J = 7.7 Hz), 131.7 (d, J = 3.2 Hz), 125.7 (q, J = 288 Hz), 114.7 (d, J = 23 Hz), 113.2 (d, J = 20 Hz), 77.5, 75.1 (q, J = 27 Hz), 72.9 (q, J = 0.8 Hz), 40.3, 38.7 (d, J = 1.3 Hz), 31.3, 30.8, 25.4 (q, J = 1.64 Hz), 22.6. **HRMS-ESI** $C_{16}H_{18}F_4O$ calcd for $[M + H]^+$ 303.1367 found 303.1343.

(*R*)-6-(2-Methylphenyl)-6-methyl-4-(trifluoromethyl)-1-(trimethylsilyl)hept-1-yn-4-ol (11c). Homopropargylic alcohol (*S*)-**11c** was prepared by the general procedure for the zinc-catalyzed asymmetric propargylation with 1,1,1-trifluoro-4-(2-methylphenyl)-4-methylpentan-2-one **6c** (0.787 g, 3.22 mmol) to provide alcohol (*S*)-**11c** as a colorless oil (1.03 g, 90%) in 92:8 enantiomeric ratio determined by chiralpak OJ-RH HPLC (45% 0.1% AcOH in water to 55% MeCN, 1.2 mL/min, 220 nm) favoring the 10.13 min over the 9.58 min enantiomer. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44−7.38 (m, 1H), 7.20−7.10 (m, 3H), 2.57 (s, 3H), 2.53 (d, J = 15.7 Hz, 1H), 2.48 (d, J = 17.5 Hz, 1H), 2.34 (d, J = 17.5 Hz, 1H), 2.32 (d, J = 15.7 Hz, 1H), 2.31 (s, 1H), 1.58 (s, 3H), 1.55 (s, 3H), 0.14 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.4, 136.3, 133.5, 127.3, 126.9, 126.5, 125.7 (q, J = 287.6 Hz), 99.9, 89.7, 75.4, (q, J = 27.0 Hz), 40.5, 38.6, 31.6, 31.0, 26.8 (q, J = 1.5 Hz), 23.5, −0.21. **HRMS-ESI** $C_{19}H_{27}F_3OSi$ calcd for $[M+NH_4]+$ 374.2122 found 374.2115.

(*R*)-6-(2-Bromo-4-fluorophenyl)-6-methyl-4-(trifluoromethyl)-1-(trimethylsilyl)hept-1-yn-4-ol (11d). Homopropargylic alcohol (*R*)-**11d** was prepared by the general procedure for the zinc-catalyzed asymmetric propargylation with 4-(2-bromo-4-fluorophenyl)-1,1,1-trifluoro-4-methylpentan-2-one **6d** (1.04g, 3.2 mmol) to provide alcohol (*R*)-**11d** as a colorless oil (1.04 g, 75%) in 89:11 enantiomeric ratio favoring the 2.31 min over the 2.17 min enantiomer determined by chiralpak IA HPLC (2% IPA in heptane, 2 mL/min, 220 nm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (dd, J = 6.1, 9.0 Hz, 1H), 7.34 (dd, J = 2.8, 8.2 Hz, 1H), 7.00 (ddd, J = 2.8, 7.3, 9.0 Hz, 1H), 2.89 (d, J = 15.6 Hz, 1H), 2.45 (d, J = 15.2 Hz, 2H), 2.43 (s, 1H), 2.37 (d, J = 15.6 Hz, 1H), 1.63 (s, 3H), 1.59 (s, 3H), 0.14 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.60 (d, J = 249 Hz), 141.01 (d, J = 3.7 Hz), 130.3 (d, J = 7.9 Hz), 125.7 (q, J = 289.7 Hz), 122.9 (d, J = 24.1 Hz), 122.1 (d, J = 8.7 Hz), 114.4 (d, J = 19.6 Hz), 99.2, 90.4, 74.9 (q, J = 26.5 Hz), 39.2, 38.9, 31.0, 30.4, 26.5, −0.24. **HRMS-ESI** $C_{18}H_{23}BrF_4OSi$ calcd for $[M + NH_4]^+$ 456.0976 found 456.0975.

(*R*)-6-Methyl-6-(2-(methylthio)phenyl)-4-(trifluoromethyl)-1-(trimethylsilyl)hept-1-yn-4-ol (11e). Homopropargylic alcohol (*R*)-**11e** was prepared by the general procedure for the zinc-catalyzed asymmetric propargylation with 1,1,1-trifluoro-4-methyl-4-(2-(methylthio)phenyl)pentan-2-one **6e** (0.829 g, 3.0 mmol) to provide alcohol (*R*)-**11e** as a colorless oil (0.980g, 84%) in 93:7 enantiomeric ratio favoring the 2.44 over the 2.32 min enantiomer determined by chiralpak IA HPLC (0.2% IPA in heptane, 2 mL/min, 220 nm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 1.5, 7.7 Hz, 1H), 7.33 (dd, J = 1.5, 7.8 Hz, 1H), 7.22 (ddd, J = 1.7, 7.3, 7.3 Hz, 1H), 7.16 (ddd, J = 1.6, 7.4, 7.4 Hz, 1H), 2.90, (d, J = 15.4 Hz, 1H), 2.64 (s, 1H), 2.60 (d, J = 15.6 Hz, 1H), 2.52 (s, 3H), 2.51 (d, J = 17.8 Hz, 1H), 2.39 (d, J = 17.5 Hz, 1H), 1.63 (s, 3H), 1.62 (s, 3H), 0.14 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.6, 137.1, 129.7, 127.6, 127.2, 126.0, 125.8 (q, J = 286.7 Hz), 100.0, 89.7, 75.4, (q, J = 25.7 Hz), 40.9, 39.0, 31.4, 30.9, 26.2, 18.2, −0.21. **HRMS-ESI** $C_{19}H_{27}F_3OSSi$ calcd for $[M + NH_4]^+$ 406.1842 found 406.1842.

(*R*)-6-(5-Bromo-2-methoxyphenyl)-6-methyl-4-(trifluoromethyl)-1-(trimethylsilyl)hept-1-yn-4-ol (11f). Homopropargylic alcohol (*R*)-**11f** was prepared by the general procedure for the zinc-catalyzed asymmetric propargylation with 4-(5-bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methylpentan-2-one **6f** (1.02 g, 3.0 mmol) to provide alcohol (*R*)-**11f** as a slightly yellow oil (1.28 g, 94%) in 91:9 enantiomeric ratio favoring the 3.09 over the 2.42 min enantiomer determined by chiralpak AD-H HPLC of the terminal alkyne derivative after proto-desilylation with potassium carbonate in methanol (10% IPA in heptane, 2 mL/min, 210 nm). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (d, J = 2.75 Hz, 1H), 7.32 (dd, J = 2.4, 8.6 Hz, 1H), 6.75 (d, J = 8.70 Hz, 1H), 3.83 (s, 3H), 2.57 (d, J = 15.3 Hz, 1H), 2.50 (s, 1H), 2.48 (d, J = 17.2 Hz, 1H), 2.42 (d, J = 15.3 Hz, 1H), 2.34 (d, J = 17.2 Hz, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 0.15 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.1, 137.7, 130.63, 130.5, 125.7 (q, J = 287 Hz), 113.6, 113.2, 99.9, 89.8, 75.0 (q, J = 26.2 Hz), 55.2, 39.9, 37.5, 30.7, 30.0, 26.5, −0.20. **HRMS-ESI** $C_{19}H_{26}BrF_3O_2Si$ calcd for $[M + NH_4]^+$ 468.1176 found 468.1177.

(*S*)-2-(4-(Dimethylamino)phenyl)-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-yn-2-ol (11g). Homopropargylic alcohol (*R*)-**11g** was prepared by the general procedure for the zinc-catalyzed asymmetric propargylation with 1-(4-(dimethylamino)phenyl)-2,2,2-trifluoroethanone **6g** (0.625 g, 2.9 mmol) to provide alcohol (*R*)-**11g** as a colorless oil (0.867 g, 91%) in 86:14 enantiomeric ratio favoring the 3.65 over the 3.34 min enantiomer determined by chiralpak AD-H HPLC (1% IPA in heptane, 2 mL/min, 220 nm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.9 Hz, 2H), 3.13 (d, J = 17.1 Hz, 1H), 3.07 (bs, 1H), 3.00 (d, J = 17.1 Hz, 1H), 2.97 (s, 6H), 0.10 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.6, 127.1, 125.2 (q, J = 286 Hz), 123.7, 111.7, 99.1, 90.7, 74.9 (q, J = 28.5 Hz), 40.3, 28.9, −0.24. **HRMS-ESI** $C_{16}H_{22}F_3NOSi$ calcd for $[M + H]^+$ 330.1510 found 330.1491.

(*S*)-1,1,1-Trifluoro-2-(3-(trifluoromethyl)phenyl)-5-(trimethylsilyl)pent-4-yn-2-ol (11h). Homopropargylic alcohol (*R*)-**11h** was prepared by the general procedure for the zinc-catalyzed asymmetric propargylation with 2,2,2-trifluoro-1-(3-(trifluoromethyl)-phenyl)ethanone **6h** (0.726 g, 3.0 mmol) to provide alcohol (*R*)-**11h** as a colorless oil (0.887 g, 83%) in 81:19 enantiomeric ratio favoring the 2.72 over the 3.04 min enantiomer determined by chiralpak OJ-H HPLC (2% IPA in heptane, 2 mL/min, 220 nm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.54 (dd, J = 7.6, 7.7 Hz, 1H), 3.19 (s, 1H), 3.17 (d, J = 17.3 Hz, 1H), 3.06 (d, J = 17.3 Hz, 1H), 0.65 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.8, 130.8 (q, J = 32 Hz), 129.8, 128.8, 125.7 (q, J = 3.7 Hz), 124.7 (q, J = 287 Hz), 124.1 (q, J = 273 Hz), 123.5 (q, J = 3.4 Hz), 97.6, 91.8, 75.1 (q, J = 28 Hz), 29.1, −0.44. **HRMS-ESI** $C_{15}H_{16}F_6OSi$ calcd for $[M + TFA]^-$ 467.0731 found 467.0728.

(*S*)-2-(4-Chlorophenyl)-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-yn-2-ol (11i). Homopropargylic alcohol (*S*)-**11i** was prepared by the general procedure for the zinc-catalyzed asymmetric propargylation with 1-(4-chlorophenyl)-2,2,2-trifluoroethanone **6i** (0.626 g, 3.0 mmol) to provide alcohol (*S*)-**11i** as a colorless oil (0.671 g, 70%) in 85:15 enantiomeric ratio determined by chiralcel OJ-RH HPLC (45% 0.1 AcOH in water pH adjusted to 4.5 with NH_4OH and 55% MeCN, 1.2 mL/min, 220 nm) favoring the 6.43 min over the 5.46 min enantiomer. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 3.14 (d, J = 17.3 Hz, 1H), 3.15 (bs, 1H), 3.00 (d, J = 17.3 Hz, 1H), 0.09 (s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.2, 135.0, 128.5, 127.9, 124.7 (q, J = 284.8), 98.0, 91.6, 74.9 (q, J = 28.8), 29.0 (q, J = 1.5 Hz), −0.32. **HRMS-ESI** $C_{14}H_{16}ClF_3OSi$ calcd for $[M + TFA]^-$ 433.0467 found 433.0436.

(*R*)-1-Phenyl-3-(trifluoromethyl)-6-(trimethylsilyl)hex-5-yn-3-ol (11j). Homopropargylic alcohol (*R*)-**11j** was prepared by the general procedure for the zinc-catalyzed asymmetric propargylation with 1,1,1-trifluoro-4-phenylbutan-2-one **6j** (0.606 g, 3.0 mmol) to provide alcohol (*R*)-**11j** as a colorless oil (0.836 g, 89%) in 80:20 enantiomeric ratio favoring the 4.27 over the 3.88 min enantiomer determined by chiralpak IA HPLC (1.5% IPA in heptane, 2 mL/min, 210 nm). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29−7.24 (m, 2H), 7.21−7.16 (m, 3H), 2.75 (t, J = 8.6 Hz, 2H), 2.71 (s, 2H), 2.55 (s, 1H), 2.16−2.00 (m, 2H), 0.16 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.1, 128.6, 128.3, 126.2, 125.8, (q, J = 287 Hz), 99.0, 90.1, 74.0, (q, J = 27.3 Hz), 35.84, 29.1 (q, J = 1.1 Hz), 26.2 (q, J = 1.7 Hz), −0.20. **HRMS-ESI** $C_{16}H_{21}F_3OSi$ calcd for $[M + NH_4]^+$ 332.1652 found 332.1641.

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■ ASSOCIATED CONTENT

Supporting Information

Preparation of pinacol boronic acid, and experimental details for kinetic analysis, computation analysis, and DoE. Copies of ^{1}H and ^{13}C for all products and chromatographs for diastereomeric and enantiomeric ratio determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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