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Chiral Propargyl Alcohols via the Enantioselective Addition of Terminal Di- and Triynes to Aldehydes

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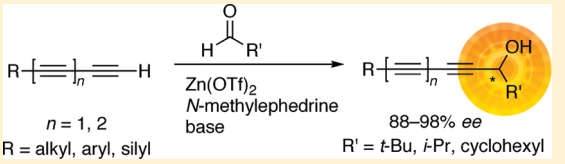
Supporting Information

ABSTRACT: The enantioselective addition of di- and triynes to aldehydes is presented, including the first examples of an asymmetric triyne addition. Modification of the Carreira alkynylation protocol shows that addition of diynes and triynes to α-branched aldehydes can be complete in as little as 4 h, and these reactions give good yields and enantioselectivities (up to 98% ee) for di- and triynes tested (aryl, alkyl, and silyl). It is shown for two cases (**20** and **24**) that products of this asymmetric addition reaction can undergo further manipulation (desilylation and triazole formation) without affecting the enantiopurity.



INTRODUCTION

Hundreds of acetylenic natural products have been isolated, and many of these compounds feature a propargylic alcohol.[1] The diversity of natural sources that produce such polyynols is impressive and includes plants, fungi, corals, sponges, and bacteria. Equally remarkable is the structural variation of the polyynol framework, and di-, tri-, tetra-, and pentaynols have been isolated to date. Finally, from this class of natural products, many members have been shown to be biologically active.[2]

Several examples are used to express these points. The diynes falcarindiol and panaxytriol (**1** and **2**, respectively, Figure 1), have both been isolated from species of *Panax*,[3] a class of plants long used in traditional medicine. These compounds show a range of properties, including inhibitory effects against methicillin-resistant strains of *Staphylococcus aureus* and the growth of B16 melanoma cells.[4] A structurally similar C_{17} compound, virol B (**3**) is a toxic component found within water hemlock (*Cicuta virosa*).[5] The unusual triyne natural product L-660,631 (**4**) is isolated from *Actinomycetes* fermentation broth[6] and *Microbispora*,[7] and it shows good in vitro activity against *Candida albicans* and dermatophytic fungi.[8] Tetrayne minquartynoic acid **5** has been isolated from the bark of a plant (*Minquartia guianensis*) traditionally used as an anthelmintic in Ecuador.[9] This polyyne is highly cytotoxic against 10 different tumor cell lines[10] and shows anti-HIV properties.[11] Finally, the pentayne glucoside **6** has been first isolated from *Microglossa pyrifolia*[12a] and, most recently, along with its aglycone from *Bidens pilosa*.[12b] The aglycone of **6** shows highly potent antimalarial and antibacterial properties in vitro, as well as antimalarial activity in vivo, based on intravenous injection of the drug in mice infected with the *Plasmodium berghei* NK-65 strain.[12b]

Traditionally, the most common method for incorporating an optically active propargylic alcohol moiety into a polyyne framework initiates with the creation of a propargylic alcohol building block with the desired stereochemistry.[13] Through a generally cumbersome and often low yielding process of cross-coupling reactions, extension of the acetylenic backbone is then achieved.[2d] Because the chiral building block is incorporated rather early in

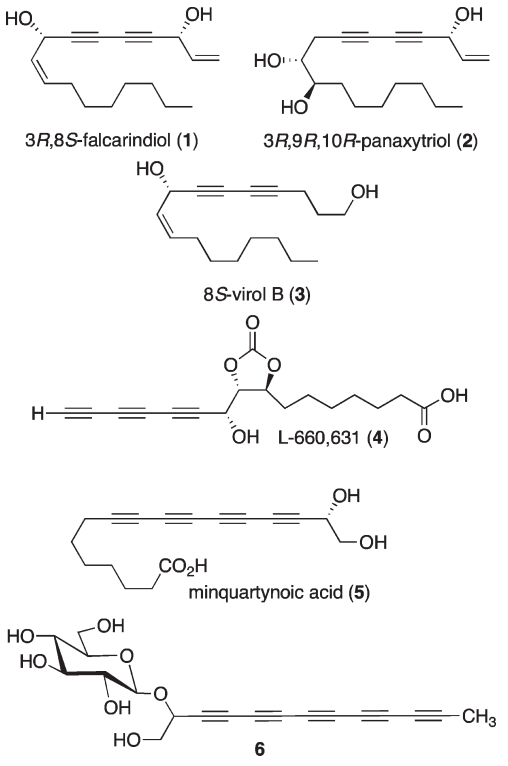


Figure 1. Examples of naturally occurring, optically active polyynes with a propargylic alcohol moiety.

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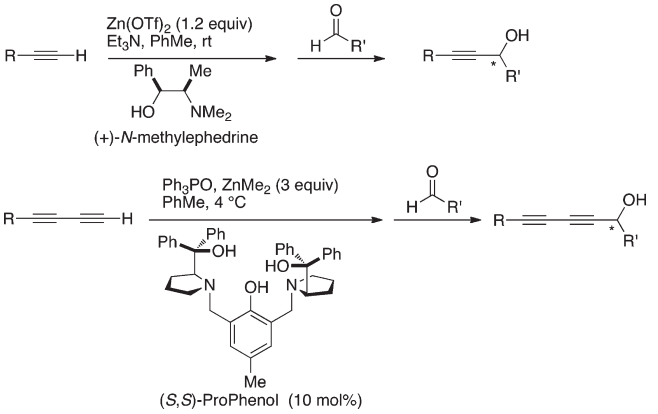
Scheme 1. Carreira (top) and Trost (bottom) Protocols for Enantioselective Propargylic Alcohol Synthesis



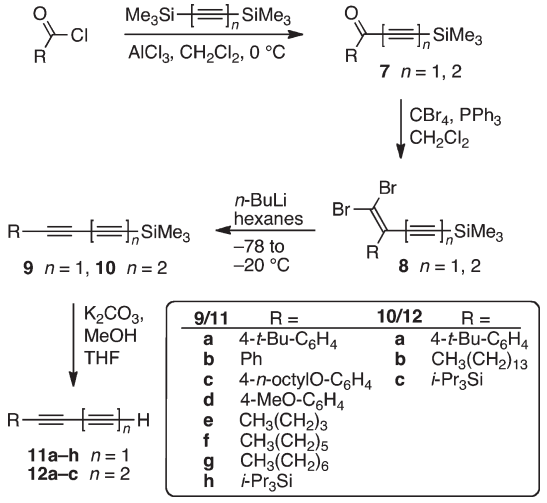
the synthesis, however, we saw this route as less efficient than a protocol in which the propargylic stereocenter is created late in the synthesis through asymmetric addition of an oligoyne to an aldehyde. Enantioselective methods are viable routes toward the asymmetric formation of chiral propargylic alcohols.[13−15] For example, the Carreira alkynylation (Scheme 1) reaction using $Zn(OTf)_2$ and *N*-methylephedrine works well with α-branched aldehydes,[14,15] although it is less efficient with unsaturated aldehydes and those that lack α-branching.[16] Since the initial report by Carreira, others have expanded on this process using variations of the *N*-methylephedrine ligand,[17] although little work has been directed toward developing conditions directly applicable to di- or triynes.[18]

More recently, Trost and co-workers have shown that the asymmetric addition of diynes to a range of aldehydes can be carried out by using dimethylzinc in the presence of the catalyst (*S*,*S*)-ProPhenol, giving propargylic alcohols in good to excellent yield and enantiomeric excess (Scheme 1).[19] The substrates that work best with the Trost protocol are α,*β*-unsaturated or non-α-branched aldehydes, i.e., the opposite trend to that observed by Carreira. To our knowledge, neither the Carreira nor the Trost protocols have been extended to the asymmetric addition of 1,3,5-hexatriynes to aldehydes. In this contribution, we outline our attempts to provide a general method for the asymmetric addition of diynes and triynes into aldehydes.

RESULTS AND DISCUSSION

Diynes and triynes used in this study have been formed via a Fritsch−Buttenberg−Wiechell (FBW) rearrangement (except for **11f**),[20−22] as schematically outlined in Scheme 2. Briefly, an acid chloride was subjected to a Friedel−Crafts acylation reaction with bis(trimethylsilyl)acetylene or -1,4-butadiyne in the presence of $AlCl_3$ to produce a ketone **7**.[23] The resulting ketone was transformed to the corresponding dibromoolefin **8** using the conditions reported by Ramirez.[24] The dibromoolefin was then subjected to a FBW rearrangement through reaction with *n*-BuLi to give either the corresponding di- or triyne (**9** or **10**) in good to excellent yield. The trimethylsilyl protecting group was removed via reaction of the di- or triyne (**9** or **10**) with K_2CO_3 in a mixture of THF and MeOH. Due to their intrinsic instability, the resulting terminal polyyne (**11** or **12**) was, following workup, carried on immediately to the asymmetric addition reaction.

Scheme 2. Schematic Outline of the Synthesis of Di- and Triynes 11 and 12



Initial synthetic explorations using the Carreira protocol for addition to aldehydes used *t*-Bu-phenyl end-capped diyne **11a** as a substrate due to its stability in comparison to other diyne derivatives. The results are summarized in Table 1. When the reaction was performed with α-branched aldehydes, isobutyraldehyde and cyclohexanecarboxaldehyde, products **13a** and **13b** were formed in good yield and enantioselectivities of 90−95%. When the more sterically hindered pivalaldehyde was used, the yield dropped significantly for **13c**, but the enantioselectivity remained similar (90% ee) to that of **13a**,**b**. On the other hand, when the reaction was done with the non-α-branched aldehyde propanal to give **13d**, a significantly lower enantioselectivity resulted (64% ee), consistent with that previously observed for monoynes.[15b] Reactions of **11a** with the α,*β*-unsaturated aldehydes acrolein or (*E*)-4-methylpent-2-enal were not successful, giving numerous byproducts and <20% yield of the desired products as estimated by ^{1}H NMR spectroscopy. Enantiomers of the *N*-methylephedrine ligand gave equal enantioselectivities with the opposite optical rotation (e.g., **13a** and **13c**, entries 1 and 2, and 4 and 5), as expected. Finally, it is worth noting that the presence of water in the reaction media led to a dramatic lowering of the observed enantioselectivity of the reaction.

Typical reaction times required for completion of the test reactions were 72 h, which is less than ideal for reactions with terminal polyynes. A number of factors were thus examined toward optimizing the rate of the reaction using alkyne **11a** and isobutyraldehyde (Table 2). Increasing the amount of $Zn(OTf)_2$ from 1.2 to 1.6 equiv cut the reaction time nearly in half, while yields and enantioselectivities held steady. Further increasing the amount of $Zn(OTf)_2$ to ca. 2.2 equiv had little effect on either yield or enantioselectivity (entries 3 and 4).

The effect of temperature was then explored. When heated to 40 °C, using 1.6 equiv of $Zn(OTf)_2$, a yield of 89% was obtained with 92% ee in only 13 h (entry 5). When the reaction was performed at higher temperatures (entries 6−8), significant decreases in enantioselectivity were observed. The ideal reaction conditions were thus suggested as 1.6 equiv of $Zn(OTf)_2$ with heating to 40 °C. Due to the instability of most terminal diynes, however, there was hesitation to use heat when exploring the scope of diynes for this reaction. Since heating the reaction

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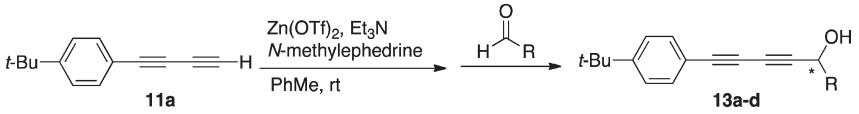
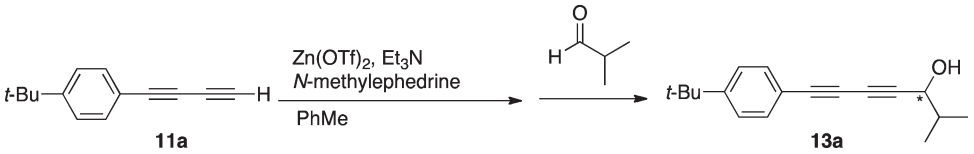
Table 1. Reaction of Diyne 11a with Various Aldehydes[a]



entry	ligand[b]	R	product[c]	yield,[d] %	% ee
1	(1*R*, 2*S*)	*i*-Pr	(*S*)-(+)-**13a**	89	95[e]
2	(1*S*,2*R*)	*i*-Pr	(*R*)-(−)-**13a**	83	94[e]
3	(1*R*,2*S*)	*c*-C_6H_{12}	(*S*)-(+)-**13b**	73	90[f]
4	(1*S*,2*R*)	*t*-Bu	(*R*)-(−)-**13c**	33	90[e]
5	(1*R*,2*S*)	*t*-Bu	(*S*)-(+)-**13c**	37	90[e]
6	(1*R*,2*S*)	Et	(*S*)-(−)-**13d**	45	64[f]

[a] Reaction conditions: Alkyne (1.2 equiv), $Zn(OTf)_2$ (ca. 1.2 equiv), *N*-methylephedrine (ca. 1.2 equiv), Et_3N (ca. 1.2 equiv), aldehyde (1 equiv); ca. 0.5 mmol scale, PhMe (1 mL). [b] Ligand (1*R*,2*S*)-(−)- or (1*S*,2*R*)-(+)-*N*-methylephedrine. [c] Absolute stereochemistry established by Mosher ester method. [d] Isolated yields. [e] Enantioselectivity calculated via HPLC analysis. [f] Enantioselectivity calculated via the modified Mosher method.

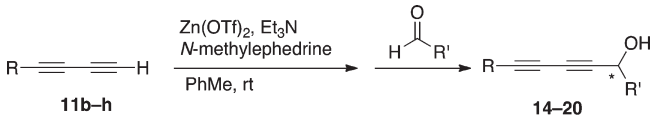
Table 2. Results toward Optimizing Reaction Time[a]



entry	$Zn(OTf)_2$, equiv	ligand[b]	temp/°C	time/h	product[c]	yield,[d] %	% ee[e]
1	1.2	(1*R*,2*S*)	rt	72	(*S*)-(+)-**13**	89	95
2	1.6	(1*R*,2*S*)	rt	37	(*S*)-(+)-**13**	82	94
3	2.2	(1*S*,2*R*)	rt	36	(*R*)-(−)-**13**	83	94
4	2.1	(1*S*,2*R*)	37	48	(*R*)-(−)-**13**	79	93
5	1.6	(1*S*,2*R*)	40	13	(*R*)-(−)-**13**	89	92
6	1.6	(1*S*,2*R*)	50	14	(*R*)-(−)-**13**	89	73
7	1.6	(1*S*,2*R*)	60	3	(*R*)-(−)-**13**	88	58
8	1.6	(1*S*,2*R*)	80	2.5	(*R*)-(−)-**13**	89	53

[a] Reaction conditions: Alkyne (1.2 equiv), *N*-methylephedrine (ca. 1.2 equiv), Et_3N (ca. 1.2 equiv), isobutyraldehyde (1 equiv); ca. 0.5 mmol scale, PhMe (1 mL). [b] Ligand (1*R*,2*S*)-(−)- or (1*S*,2*R*)-(+)-*N*-methylephedrine. [c] Absolute stereochemistry established by Mosher ester method. [d] Isolated yields. [e] Enantioselectivity calculated via HPLC analysis.

Table 3. Substrate Scope for Diyne Addition to α-Branched Aldehydes[a]



diyne	R	ligand[b]	R′	product[c]	yield,[d] %	% ee
11b	Ph	(1*S*,2*R*)	*i*-Pr	(*R*)-(−)-**14**	88	92[e]
11c	4-*n*-octylO-C_6H_4	(1*R*,2*S*)	*c*-C_6H_{12}	(*S*)-(+)-**15**	82	97[f]
11d	4-MeO-C_6H_4	(1*R*,2*S*)	*i*-Pr	(*S*)-(+)-**16**	93	98[e]
11e	$CH_3(CH_2)_3$	(1*S*,2*R*)	*i*-Pr	(*R*)-(−)-**17**	43	88[f]
11f	$CH_3(CH_2)_5$	(1*R*,2*S*)	*i*-Pr	(*S*)-(+)-**18**	65	93[f]
11g	$CH_3(CH_2)_6$	(1*R*,2*S*)	*i*-Pr	(*S*)-(+)-**19**	77	90[f]
11h	*i*-Pr_3Si	(1*R*,2*S*)	*i*-Pr	(*S*)-(+)-**20**	89	91[e]

[a] Reaction conditions: Alkyne (1.2 equiv), $Zn(OTf)_2$ (ca. 1.6 equiv), *N*-methylephedrine (ca. 1.2 equiv), Et_3N (ca. 1.2 equiv), aldehyde (1.0 equiv); ca. 0.5 mmol scale, PhMe (1 mL). [b] Ligand (1*R*,2*S*)-(−)- or (1*S*,2*R*)-(+)-*N*-methylephedrine. [c] Absolute stereochemistry established by Mosher ester method. [d] Isolated yields. [e] Enantioselectivity calculated via HPLC analysis. [f] Enantioselectivity calculated via the modified Mosher method.

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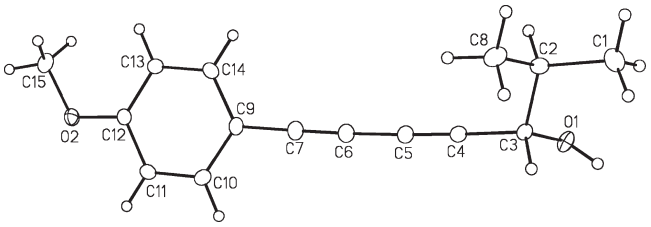


Figure 2. ORTEP drawing of **16** (20% probability level).

helped increase the rate of the reaction, but had no effect toward increasing enantioselectivities, it was ultimately decided to vary the diynes while continuing to perform these reactions at room temperature.

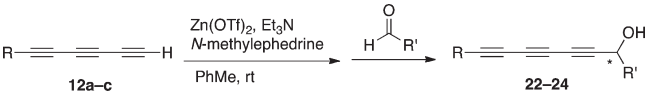
The scope of the reaction was then explored using diynes **11b**−**h** in reactions with α-branched aldehydes cyclohexanecarboxaldehyde and isobutyraldehyde. Enantioselectivities ranging from 88% to 98% ee, in typically respectable yields were obtained (Table 3). Arylbutadiynes **11b**−**d** reacted with aldehydes to give products **14**−**16** in excellent yield, and in good (92%) to excellent (98%) ee. Alkyl-substituted diynes also worked well, giving propargylic alcohols **17**−**19** with 88−93% ee and increasing yields as a function of length of the alkyl chain. The observed increase in yield is likely related to the stability of the terminal diynes during the desilylation step, i.e., the longer the alkyl chain the greater the stability of the terminal polyyne. Finally, the reaction of the triisopropylsilyl diyne **11h** with isobutyraldehyde gave **20** in 89% yield and 91% ee. Given the ability to remove the *i*-Pr_3Si-group of **20** with a fluoride source, compound **20** offers a potential building block for other chiral derivatives (vide infra).

Crystals of **16** suitable for X-ray diffraction have been obtained from a concentrated solution of diethyl ether at room temperature (Figure 2) and offer a chance to explore structure and, potentially, stereochemistry at C3. Crystallographic analysis shows that bond angles and lengths for **16** are unremarkable. While the structure suggests an (*S*)-configuration at C3, the obtained Flack parameter was not sufficient to assign reliably the absolute stereochemistry.[25] Formation of (*S*)-**16** is, however, expected when using (1*R*,2*S*)-(−)-*N*-methylephedrine based on literature reports.[26] Furthermore, the stereochemistry at C3 was confirmed experimentally by synthesis of both the (*R*)- and (*S*)-Mosher esters of **16** and analysis of their ^{1}H NMR spectra (see Supporting Information). Likewise, Mosher ester formation and product analysis by ^{1}H NMR spectroscopy was used to confirm the stereochemistry for other alcohols formed in this study (see Supporting Information).

Encouraging results with the asymmetric addition of diynes to aldehydes led to the examination of reactions with triynes. Due to the intrinsic instability typically observed for terminal triynes (even in solution), however, their use as starting materials is more challenging than the corresponding diynes.[27] Nevertheless, these examples establish the viability of this route. The reaction of triyne **12a** with isobutyraldehyde and cyclohexanecarboxaldehyde gave products **21** and **22** with similar enantioselectivities (Table 4). The yield of **22** was, however, lower as observed in the analogous reaction of diyne **11a** with cyclohexanecarboxaldehyde. The reaction of 1,3,5-icosatriyne **12b** with isobutyraldehyde gave **23** in a good yield (80%) and enantioselectivity (89% ee), and the triisopropylsilyl-terminated triyne **12c** gave **24** in comparable yield.

Unfortunately, the enantiomers of **24** were inseparable by xHPLC, and attempted Mosher ester formation was not efficient;

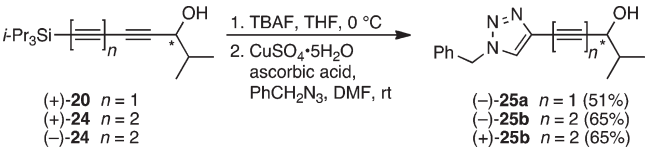
Table 4. Substrate Scope for Triyne Addition to α-Branched Aldehydes[a]



triyne	R	ligand[b]	R′	product[c]	yield,[d] %	% ee
12a	4-*t*-Bu-C_6H_4	(1*R*,2*S*)	*i*-Pr	(*S*)-(+)-**21**	69	89[e]
12a	4-*t*-Bu-C_6H_4	(1*R*,2*S*)	*c*-C_6H_{12}	(*S*)-(+)-**22**	36	90[e]
12b	$CH_3(CH_2)_{13}$	(1*S*,2*R*)	*i*-Pr	(*R*)-(−)-**23**	80	89[e]
12c	*i*-Pr_3Si	(1*S*,2*R*)	*i*-Pr	(*R*)-(−)-**24**	78	94[f]
12c	*i*-Pr_3Si	(1*R*,2*S*)	*i*-Pr	(*S*)-(+)-**24**	81	98[f]

[a] Reaction conditions: Alkyne (1.2 equiv), $Zn(OTf)_2$ (ca. 1.6 equiv), *N*-methylephedrine (ca. 1.2 equiv), Et_3N (ca. 1.2 equiv), aldehyde (1.0 equiv); ca. 0.5 mmol scale, PhMe (1 mL). [b] Ligand (1*R*,2*S*)-(−)- or (1*S*,2*R*)-(+)-*N*-methylephedrine. [c] Absolute stereochemistry established by Mosher ester method. [d] Isolated yields. [e] Enantioselectivity calculated via the modified Mosher method. [f] Enantioselectivity based on derivatization; see Scheme 3.

Scheme 3. [a] **Triazole Formation Using Diyne 20 and Triyne 24**

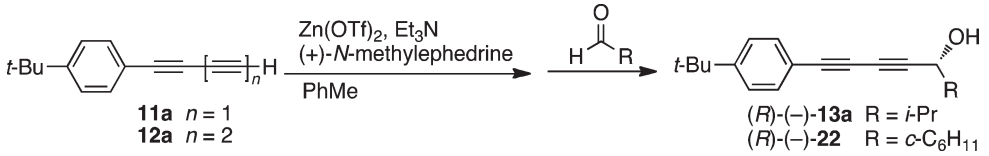


thus, the enantiomeric excess could not be established directly for **24**. As with diyne **20**, triyne **24** is also a masked terminal acetylene, which allows for further functionalization. To establish this possibility, the triisopropylsilyl-group of (*S*)-(+)-**20** (91% ee) was removed using TBAF, and, after aqueous workup, the resulting terminal diyne was trapped with benzyl azide[28] via a CuAAC reaction[29] to give the 1,4-disubstituted 1,2,3-triazole product (*S*)-(−)-**25a** in a 51% yield and a 91% ee (Scheme 3). In an analogous reaction sequence, triyne (*S*)-(+)-**24** gave (*S*)-(−)-**25b** in a 65% yield and 98% *ee*, while (*R*)-(−)-**24** gave (*R*)-(+)-**25b** with similar results. This suggests that (*S*)-(+)- and (*R*)-(−)-**24** were formed initially with 98% and 94% ee, respectively, and that the removal of the silyl protecting group and further functionalization does not appear to impact enantiopurity.

As our work was nearing completion, a recent publication by Trost and co-workers appeared,[19] which described rate enhancement and increased enantioselectivities using additives such as triphenylphosphine oxide, prompting us to explore such effects in our protocol. In comparison to our initial result (Table 5, entry 1), using triphenylphosphine oxide as an additive in the reaction of **11a** with isobutyraldehyde gave a slight decrease in the reaction time, and the enantioselectivity also decreased slightly (Table 5, entry 2).

When using acetylene as an alkyne source for asymmetric addition to aldehydes, Carreira reported the use of the slightly stronger Hunig's base (*i*-Pr_2NEt) in place of Et_3N.[30] In the present study, reaction times decreased somewhat with Hunig's base, while the enantioselectivity increased slightly (entry 3). When triphenylphosphine oxide was used in conjunction with

Table 5. The Effect of PPh_3O Additive and Base on Formation of (*R*)-(−)-13 and -22[a]



entry	product	base	additive	time/h	yield,[b] %	% ee[c]
1	(*R*)-(−)-**13**	Et_3N	–	36	83	94
2	(*R*)-(−)-**13**	Et_3N	PPh_3O (1 equiv)	20	79	88
3	(*R*)-(−)-**13**	*i*-Pr_2NEt	–	19	80	98
4	(*R*)-(−)-**13**	*i*-Pr_2NEt	PPh_3O (1 equiv)	20	79	95
5	(*R*)-(−)-**13**	*i*-Pr_2NEt	PPh_3O (0.2 equiv)	20	83	97
6	(*R*)-(−)-**13**	*i*-Pr_2NEt	–	4[d]	83	95
7	(*R*)-(−)-**22**	*i*-Pr_2NEt	–	30	52	94

[a] Reaction conditions: Alkyne (1.2 equiv), $Zn(OTf)_2$ (ca. 1.6 equiv), (1*S*,2*R*)-(+)-*N*-methylephedrine (ca. 1.2 equiv), base (ca. 1.2 equiv), aldehyde (1.0 equiv): ca. 0.5 mmol scale, PhMe (1 mL), rt. [b] Isolated yields. [c] Enantioselectivity calculated via HPLC. [d] Reaction was performed at 40 °C.

Hünig's base, the enantioselectivity remained approximately constant (entries 4 and 5). With Hünig's base and heating to 40 °C, the reaction was complete in 4 h to give an 83% yield and a 95% ee (Table 5, entry 6). While these optimizations suggest a means to decrease the reaction time, yields and enantioselectivities remained more or less constant. As a final test, the reaction of **12a** with cyclohexanecarboxaldehyde was examined, since this reaction was the most challenging of those attempted with triynes (see Table 4). The result was encouraging: the yield (from 36 to 52%) and enantioselectivity (from 90 to 94%) increased somewhat, while the reaction time decreased from 90 to 30 h.

CONCLUSIONS

In summary, the asymmetric addition of terminal diynes and triynes to aldehydes described herein provides a direct route to obtain optically active propargylic alcohols, often with good to excellent yields and enantioselectivities. This method works best with α-branched aldehydes, and it is thus complementary to the recently published Trost protocol. This study offers the first examples of asymmetric triyne addition to an aldehyde and establishes that the length of the polyyne has little effect on enantioselectivity, although yields do trend lower for triynes, which is likely a result of decreased stability of the terminal triyne precursor. Two factors, however, appear to offer a means to improve the success of asymmetric addition reactions of triynes to aldehydes: (1) the use of Hunig's base and (2) Trost conditions with the ProPhenol ligand. These protocols are now being examined.

EXPERIMENTAL SECTION

General Details. Procedures for the synthesis of compounds **9a**,[22c] **9b**,[22a] **9c**,[31] **9d**,[22c] **9e**,[22a] **9f**,[32] **9h**,[28b] **10a**,[22c] and **10c**[22b] have been reported. All reactions were performed in standard, dry glassware under an inert atmosphere of N_2. Unless otherwise specified, reagents were purchased from commercial suppliers and used without further purification. PhMe was distilled from sodium/benzophenone ketyl, while hexanes and dichloromethane were distilled from CaH_2 immediately prior to use. Anhydrous $MgSO_4$ was used as the drying agent after aqueous workup. $Zn(OTf)_2$ was dried in a Schlenk flask under vacuum (ca. 1 mmHg) for at least 12 h, while heating to 100 °C to remove water. Cyclohexanecarboxaldehyde and isobutyraldehyde were dried over $CaSO_4$ and fractionally distilled directly before use. Pivalaldehyde and propionaldehyde were dried over $CaCl_2$ and fractionally distilled directly before use. Evaporation and concentration in vacuo were done at H_2O-aspirator pressure. Column chromatography: silica gel-60 (230−400 mesh). Thin layer chromatography (TLC): precoated plastic sheets covered with 0.2 mm silica gel with fluorescent indicator UV 254 nm; visualization by UV light, $KMnO_4$ or anisaldehyde stain. IR spectra (cm^{-1}, cast film or neat). ^1H, ^{19}F, and ^{13}C NMR: 300, 400, 500, and 700 MHz instruments, at 27 °C in CD_2Cl_2, $CDCl_3$, $(CD_3)_2CO$, or CD_3CN; solvent peaks (5.32, 7.26, 2.05, and 1.96 ppm, respectively, for ^1H; 53.8, 77.0, 206.26/29.84, and 118.26/1.32 ppm, respectively, for ^{13}C) as reference. Optical rotations were recorded on a polarimeter using the sodium D line (589 nm) with a cell length of 10.002 cm. For simplicity, the coupling constants of the aryl protons for para-substituted phenyl groups have been reported as pseudo first-order, even though they are second-order spin systems. For mass spectral analyses, low-resolution data is provided in cases when M^+ is not the base peak; otherwise, only high-resolution data are provided. Optical purities of the products were measured by chiral HPLC using either a Chiralcel OD or Chiralpak AS column or by formation of the Mosher ester and subsequent ^1H or ^{19}F NMR analysis of the product along (see Supporting Information for HPLC traces and spectra).

X-ray Crystallographic Data for 16. $C_{15}H_{16}O_2$, M_w = 228.28; crystal dimensions 0.58 × 0.53 × 0.26 mm; crystal system: orthorhombic; space group $P2_12_12_1$ (No. 19); a = 5.08550(10) Å, b = 9.6271(3) Å, c = 25.6576(7) Å; V = 1256.16(6) $Å^3$; Z = 4; ρ_{calcd} = 1.207 g cm^{-3}; μ = 0.079 mm^{-1}; λ = 0.71073 Å; T = −100 °C; $2\theta_{max}$ = 55.06°; total data collected = 11130; R_1 = 0.0312 for 1683 observed reflections with $[F_o^2 \geq 2\sigma(F_o^2)]$; wR_2 = 0.0872 for 155 variables and all 1721 unique reflections; residual electron density = 0.199 and −0.158 e $Å^{-3}$. CCDC 818624.

General Procedure. *Removal of Trimethylsilyl Groups.* To the appropriate silyl-protected diyne or triyne (0.60 mmol) in a solution of wet MeOH/THF (5 mL, 4:1 v/v) was added K_2CO_3 (6 mg, 0.04 mmol), and the mixture was stirred at rt until TLC analysis no longer showed the presence of the starting material, ca. 0.5−1.5 h. Et_2O (30 mL) and saturated aq NH_4Cl (30 mL) were added, the organic layer was separated, washed with saturated aq NH_4Cl (2 × 30 mL), dried over $MgSO_4$, and filtered, and the solvent volume was reduced in vacuo to ca. 5 mL. PhMe (0.5 mL) was added, and the remainder of the Et_2O was then removed in vacuo (taking care not to reduce the solution to

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dryness, which results in partial decomposition of the terminal polyyne). The terminal diyne/triyne in PhMe solvent was then used directly in the asymmetric addition reaction.

General Procedure. *Asymmetric Diyne and Triyne Addition to Aldehydes.* $Zn(OTf)_2$ (0.90 mmol, 1.6 equiv) and *N*-methylephedrine (0.65 mmol, 1.2 equiv) were charged under N_2 for 10 min in a 10 mL round-bottom flask. PhMe (1 mL) and Et_3N (90 μL, 0.65 mmol, 1.2 equiv) were then added. The mixture was stirred for 2 h at rt, followed by the addition of the terminal diyne/triyne (0.60 mmol, 1.1 equiv) in PhMe (0.5 mL). The flask containing the diyne was then washed with additional PhMe (0.5 mL), which was added to the reaction flask. The reaction was stirred for 20 min, and freshly purified aldehyde (0.55 mmol, 1.0 equiv) was added. The reaction was stirred at rt until deemed complete by TLC analysis. The reaction was quenched via the addition of saturated aq NH_4Cl (3 mL) and extracted with Et_2O (30 mL). The aqueous layer was further extracted with Et_2O (4 × 30 mL). The combined organic phase was dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. Unless otherwise stated, column chromatography (silica gel, hexanes/EtOAc 5:1) afforded the product.

General Procedure. *Synthesis of the Racemic Propargylic Alcohol Polyynes.* Following the removal of the silyl protecting group as per the general procedure, the appropriate di- or triyne (1 equiv) in PhMe was combined with 50 mL of hexanes. The reaction was cooled to −78 °C, and BuLi (2.5 M in hexanes, 1.2 equiv) was added. The reaction was stirred and then slowly warmed to −20 °C over 0.5 h. The solution was then cooled to −78 °C and the corresponding aldehyde (1 equiv) was added. The resulting reaction stirred while slowly warming to 0 °C over 1−2 h, until judged complete by TLC analysis. The reaction was quenched via the addition of saturated aq NH_4Cl (20 mL) and extracted with Et_2O (30 mL). The organic layer was washed with saturated aq NH_4Cl (2 × 20 mL), dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo. Column chromatography (silica gel, hexanes/EtOAc 10:1) gave the corresponding racemic diyne or triyne (30−90% yield).

General Procedure. *The Reaction of Di- and Triynes with Benzyl Azide.*[28] A mixture of the appropriate triisopropylsilyl-protected polyyne and TBAF (2.0 equiv) in THF (5 mL) was stirred at 0 °C until TLC analysis showed complete conversion to the terminal alkyne. Et_2O (25 mL) and saturated aq NH_4Cl (25 mL) were added, and the organic phase was separated, washed with saturated aq NH_4Cl (2 × 10 mL) and saturated aq NaCl (10 mL), and then dried over $MgSO_4$. DMF (1 mL) was then added and the solution concentrated to 1−2 mL via rotary evaporation. To the mixture above was added DMF (10 mL), followed by benzyl azide (1.0 equiv based on the starting silylated polyyne), $CuSO_4 \cdot 5H_2O$ (0.1 g), ascorbic acid (0.1 g), and H_2O (2 mL). This mixture was then stirred at rt until TLC analysis no longer showed the presence of the terminal alkyne. Saturated aq NH_4Cl (10 mL) and Et_2O (10 mL) were added, and the organic phase was separated, washed with saturated aq NaCl (2 × 10 mL), and dried over $MgSO_4$. Purification via column chromatography gave the pure product.

General Procedure. *Mosher Ester formation.*[33] The alcohol was added to CH_2Cl_2 (1 mL) along with either the (*R*)- or (*S*)-Mosher acid chloride (1.5 equiv), DMAP (1.0 equiv), and NEt_3 (5.0 equiv). When the reaction was judged to be complete by TLC analysis, diisopropylamine (0.2 mL) was added and the mixture passed through a 1-in. silica column (in a 9-in. pipet eluted with 30% EtOAc/hexanes). The mixture was analyzed by ^{19}F and/or ^1H NMR spectroscopy to determine the diastereomeric ratio.

[3-(Dibromomethylene)-1-decynyl]trimethylsilane. Thionyl chloride (17 g, 0.14 mol) was added to octanoic acid (2.50 g, 17.5 mmol) in a dry flask protected from moisture with a drying tube containing $CaCl_2$, and the mixture was stirred at rt for 24 h. The excess thionyl chloride was removed in vacuo to provide the acid chloride. CH_2Cl_2 (100 mL) was added, and the temperature of the solution was lowered to 0 °C. Bis(trimethylsilyl)acetylene (3.00 g, 17.6 mmol) and $AlCl_3$ (2.7 g, 20 mmol) were added, and the reaction mixture was warmed to rt over 3 h. The reaction was carefully quenched by the addition of the reaction mixture to 10% HCl (50 mL) in 10 g of ice. The organic layer was separated, washed with saturated aq $NaHCO_3$ (50 mL) and NaCl (50 mL), and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude ketone was carried on to the next step.

CBr_4 (6.6 g, 20 mmol) and PPh_3 (11 g, 42 mmol) were added to CH_2Cl_2 (125 mL) and stirred for 5 min at rt. The crude ketone in 10 mL CH_2Cl_2 was slowly added to the mixture over 10 min, and the progress of the reaction was then monitored by TLC analysis until the ketone was no longer observed (ca. 30 min). Solvent was reduced to ca. 10 mL, hexanes added (125 mL), the inhomogeneous mixture filtered through a silica gel plug with hexanes, and solvent removed in vacuo to yield the desired product (4.7 g, 71% over three steps) as a yellow oil. R_f = 0.9 (hexanes/EtOAc 10:1). IR (neat) 2958 (s), 2928 (s), 2858 (s), 2153 (m-w), 1251 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (t, J = 7.6 Hz, 2H), 1.57 (quintet, J = 7.5 Hz, 2H), 1.33−1.29 (m, 8H), 0.9 (t, J = 6.9, 3H), 0.22 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.3, 103.3, 102.9, 97.6, 36.9, 31.9, 29.2, 29.0, 27.6, 22.8, 14.3, −0.1. EIMS m/z 379.9 (M^+, 12), 137.0 ($[C_4H_9Br]^+$, 65) 73.0 ($[Me_3Si]^+$, 100).

Trimethyl-1,3-undecadiynylsilane (9g). [3-(Dibromomethylene)-1-decynyl]trimethylsilane (2.53 g, 6.64 mmol) was added to hexanes (50 mL) and cooled to −78 °C. BuLi (3.2 mL of 2.5 M BuLi in hexanes, 8.0 mmol, 1.2 equiv) was added and the reaction slowly warmed to 0 °C over 1 h. The reaction was quenched via the addition of saturated aq NH_4Cl (20 mL) and extracted with Et_2O (30 mL). The organic phase was then washed with saturated aq NH_4Cl (3 × 20 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The crude product was passed through a plug of silica gel, and column chromatography (silica gel, hexanes) gave **9g** (1.3 g, 90%) as a yellow oil. R_f = 0.85 (10:1 hexanes/EtOAc). IR (neat) 2958 (s), 2930 (s), 2858 (m), 2226 (m), 2109 (m), 1251 (m), 845 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (t, J = 7.0 Hz, 2H), 1.52 (app quintet, J = 7.3 Hz, 2H), 1.41−1.26 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H), 0.18 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.6, 83.1, 80.4, 65.6, 31.8, 29.0, 28.9, 28.3, 22.8, 19.4, 14.2, −0.2. EIMS m/z 220.2 (M^+, 1), 205.1 ($[M - Me]^+$, 100). EI HRMS calcd for $C_{14}H_{24}Si$ (M^+) 220.1647, found 220.1645.

[5-(Dibromomethylene)-1,4-nonadecadiynyl]trimethylsilane. This compound was formed in the same manner as [3-(dibromomethylene)-1-decynyl]trimethylsilane above, using myristic acid and bis(trimethylsilyl)acetylene. R_f = 0.83 (10:1 hexanes/EtOAc). IR (neat) 2957 (m), 2925 (s), 2854 (s), 2225 (w), 2156 (w) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.33 (t, J = 7.0 Hz, 2H), 1.72−1.57 (m, 4H), 1.54−1.10 (m, 20H), 0.91−0.70 (m, 3H), 0.22 (s, 9H). ^{13}C NMR (500 MHz, acetone d_6) δ 115.4, 108.5, 102.5, 101.5, 99.6, 78.2, 32.7, 28.8, 23.4, 19.9, 14.4, −0.4. EIMS m/z 504.1 (M^+, 3), 502.1 (M^+, 5), 500.1 (M^+, 3), 73.0 ($[Me_3Si]^+$, 100). EI HRMS calcd for $C_{23}H_{38}{}^{81}Br_2Si$ (M^+) 504.1069, found 504.1068. Calcd for $C_{23}H_{38}{}^{79}Br^{81}BrSi$ 502.1089, found 502.1090. Calcd for $C_{23}H_{38}{}^{79}Br_2Si$ 500.1110, found 500.1104.

Trimethyl-1,3,5-eicosyltriynylsilane (10b). [5-(Dibromomethylene)-x1,4-nonadecadiynyl]trimethylsilane (0.83 g, 1.7 mmol) was added to hexanes (50 mL), cooled to −78 °C. BuLi (0.8 mL of 2.5 M BuLi in hexanes, 2.0 mmol, 1.2 equiv) was added and the reaction slowly warmed to 0 °C over 1 h. The reaction was quenched via the addition of saturated aq NH_4Cl (20 mL) and extracted with Et_2O (30 mL). The organic phase was then washed with saturated aq NH_4Cl (3 × 20 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The crude product was passed through a plug of silica gel, and column chromatography (silica gel, hexanes) gave **10b** (0.5 g, 88%) as a yellow-brown oil. R_f = 0.85 (10:1 hexanes/EtOAc). IR (film cast, $CHCl_3$) 2957 (m), 2925 (s), 2854 (s), 2212 (m), 2167 (w), 2080 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (t, J = 7.2 Hz, 2H), 1.54 (quintet, J = 7.2 Hz, 2H), 1.40−1.22 (m, 22H), 0.89 (t, J = 6.6 Hz, 3H) 0.20 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.4, 85.3, 81.0, 65.5, 62.6,

59.9, 31.9, 29.69, 29.66, 29.6, 29.44, 26.36, 29.0, 28.8, 28.0, 22.7, 19.4, 14.1, −0.5 (two signals coincident or not observed). EIMS *m*/*z* 342.3 (M^+, 2), 327.2 ($[M - Me]^+$, 9), 73.0 ($[Me_3Si]^+$, 100). EI HRMS calcd for $C_{23}H_{38}Si$ (M^+) 342.2743, found 342.2741.

Compound 13a (Table 1, entry 1). Compound **11a** (130 mg, 0.70 mmol, 1.2 equiv) was combined with $Zn(OTf)_2$ (254 mg, 0.699 mmol, 1.2 equiv), (−)-*N*-methylephedrine (118 mg, 0.658 mmol, 1.1 equiv), Et_3N (91 μL, 0.65 mmol, 1.1 equiv), and isobutyraldehyde (55 μL, 43 mg, 0.60 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 72 h to yield (*S*)-(+)-**13a** (136 mg, 89%) as a yellow semisolid. A 95% ee was determined by HPLC analysis (Chiralcel OD column, 1% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature 10 °C) T_{major} = 38.1 min, T_{minor} = 41.7 min. $[\alpha]^{22}_D$ = 3.53° (*c* = 1.00, $CHCl_3$).

The other enantiomer, (*R*)-(−)-**13a** (Table 1, entry 2), was synthesized from **11a** (109 mg, 0.598 mmol, 1.2 equiv), $Zn(OTf)_2$ (390 mg, 1.1 mmol, 2.2 equiv), (+)-*N*-methylephedrine (110 mg, 0.61 mmol, 1.2 equiv), Et_3N (84 μL, 61 mg, 0.60 mmol, 1.2 equiv), and isobutyraldehyde (46 μL, 36 mg, 0.50 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 36 h to yield (*R*)-(−)-**13a** (105 mg, 83%) as a yellow semisolid in 94% ee. $[\alpha]^{22}_D$ = −4.05° (*c* = 1.12, $CHCl_3$). R_f = 0.33 (hexanes/EtOAc 5:1). IR (film cast, $CHCl_3$): 3352 (m, broad), 3086 (w), 3038 (w), 2964 (s), 2905 (s), 2872 (s), 2239 (m), 1604 (w), 1024 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 4.31 (t, *J* = 5.8 Hz, 1H), 1.95 (app octet, *J* = 6.6, 1H), 1.83 (d, *J* = 5.9, 1H) 1.32 (s, 9H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 132.3, 125.4, 118.4, 82.0, 78.6, 72.7, 70.4, 68.5, 34.9, 34.7, 31.1, 18.1, 17.5. EIMS *m*/*z* 254.2 (M^+, 38), 211.1 ($[M - i\text{-}Pr]^+$, 100). EI HRMS calcd for $C_{18}H_{22}O$ (M^+) 254.1671, found 254.1671.

Compound 13b (Table 1, entry 3). Compound **11a** (158 mg, 0.867 mmol, 1.2 equiv) was combined with $Zn(OTf)_2$ (371 mg, 1.02 mmol, 1.4 equiv), (−)-*N*-methylephedrine (160 mg, 0.89 mmol, 1.3 equiv), Et_3N (120 μL, 89 mg, 0.88 mmol, 1.3 equiv), and cyclohexanecarboxaldehyde (85 μL, 79 mg, 0.70 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 80 h to yield (*S*)-(+)-**13b** (150 mg, 73%) as a yellow oil. A 90% ee was determined by ^{19}F NMR analysis of the corresponding ester derived from (*S*)-MTPA chloride (−72.92 ppm (major), −71.91 ppm (minor)). $[\alpha]^{22}_D$ = 11.82° (c = 1.00, $CHCl_3$). R_f = 0.4 (CH_2Cl_2/hexanes 2:1). IR (film cast, $CHCl_3$): 3346 (m, broad), 3086 (w), 3037 (w), 2928 (s), 2854 (s), 2236 (w), 1604 (w), 1503 (m), 1016 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 4.31 (t, *J* = 5.3 Hz, 1H), 2.10 (d, 4.7 Hz, 1H), 1.95−1.85 (m, 2H), 1.82−1.78 (m, 2H), 1.71−1.59 (m, 2H), 1.32−1.09 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 132.5, 125.6, 118.6, 82.4, 78.8, 72.8, 70.7, 68.0, 44.4, 35.1, 31.2, 28.7, 28.3, 26.4, 25.82, 25.86. EIMS *m*/*z* 294.2 (M^+, 21), 211.1 ($[M - C_6H_{11}]^+$, 100). EI HRMS calcd for $C_{21}H_{26}O$ (M^+) 294.1984, found 294.1985.

Compound 13c (Table 1, entry 4). Compound **11a** (97 mg, 0.52 mmol, 1.1 equiv) was combined with $Zn(OTf)_2$ (231 mg, 0.635 mmol, 1.3 equiv), (+)-*N*-methylephedrine (122 mg, 0.681 mmol, 1.4 equiv), Et_3N (83 μL, 60 mg, 0.59 mmol, 1.2 equiv), and pivalaldehyde (53 μL, 42 mg, 0.49 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 1 week to yield (*R*)-(−)-**13c** (43 mg, 33%) as a beige semisolid. An 90% ee was determined by HPLC analysis (Chiralcel OD column, 5% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C) T_{major} = 11.4 min, T_{minor} = 10.3 min. $[\alpha]^{22}_D$ = −5.23° (*c* = 0.39, $CHCl_3$).

The other enantiomer, (*S*)-(+)-**13c** (Table 1, entry 5), was synthesized from **11a** (93 mg, 0.51 mmol, 1.3 equiv), $Zn(OTf)_2$ (220 mg, 0.61 mmol, 1.6 equiv), (−)-*N*-methylephedrine (86 mg, 0.48 mmol, 1.2 equiv), Et_3N (66 μL, 48 mg, 0.47 mmol, 1.2 equiv), and pivalaldehyde (43 μL, 34 mg, 0.39 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 1 week to give (*S*)-(+)-**13c** (38 mg, 37%) as a beige semisolid in 90% ee. $[\alpha]^{22}_D$ = 3.90° (*c* = 0.21, $CHCl_3$). R_f = 0.5 (hexanes/EtOAc 5:1). IR (film cast, $CHCl_3$): 3398 (m, broad), 3037 (w), 2963 (s), 2930 (s), 2869 (m), 2244 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 4.15 (d, *J* = 5.7 Hz, 1H), 1.80 (d, *J* = 6.1 Hz, 1H), 1.31 (s, 9H), 1.04 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 132.3, 125.5, 118.4, 82.0, 78.5, 72.7, 72.0, 70.6, 36.4, 34.9, 31.1, 25.3. EIMS *m*/*z* 268.2 (M^+, 20), 253.2 ($[M - Me]^+$, 15), 211.1 ($[M - t\text{-}Bu]^+$, 100). EI HRMS calcd for $C_{19}H_{24}O$ (M^+) 268.1827, found 268.1826.

Compound 13d (Table 1, entry 6). Compound **11a** (181 mg, 0.993 mmol, 1.3 equiv) was combined with $Zn(OTf)_2$ (430 mg, 1.2 mmol, 1.5 equiv), (−)-*N*-methylephedrine (190 mg, 1.1 mmol, 1.3 equiv), Et_3N (140 μL, 1.0 mmol, 1.1 equiv), and propionaldehyde (57 μL, 46 mg, 0.79 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 68 h to give (*S*)-(−)-**13d** (86 mg, 45%) as an off white-yellow semisolid. A 64% ee was determined by ^{19}F NMR analysis of the corresponding ester derived from (*R*)-MTPA chloride (−71.99 ppm major), −72.31 ppm (minor)). $[\alpha]^{22}_D$ = −0.99° (*c* = 0.24, $CHCl_3$). R_f = 0.6 (CH_2Cl_2). IR (film cast, $CHCl_3$): 3347 (m, broad), 3086 (w), 3038 (w), 2966 (s), 2906 (m), 2873 (m), 2239 (m), 1603 (w) cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$) δ 7.43 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 4.46 (dd, *J* = 12.2, 6.3 Hz, 1H), 1.84 (d, *J* = 5.8, 1H), 1.82−1.76 (m, 2H), 1.31 (s, 9H), 1.06 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CHCl_3$) δ 152.8, 132.3, 125.5, 118.4, 82.8, 78.8, 72.6, 69.8, 64.3, 34.9, 31.1, 30.7, 9.4. EIMS *m*/*z* 240.2 (M^+, 42), 225.1 ($[M - Me]^+$, 52), 211.1 ($[M - Et]^+$, 100). EI HRMS calcd for $C_{17}H_{20}O$ (M^+) 240.1514, found 240.1516.

Compound 14. Compound **11b** (88 mg, 0.70 mmol, 1.4 equiv) was combined with $Zn(OTf)_2$ (363 mg, 1.00 mmol, 2.0 equiv), (+)-*N*-methylephedrine (134 mg, 0.748 mmol, 1.5 equiv), Et_3N (98 μL, 71 mg, 0.70 mmol, 1.4 equiv), and isobutyraldehyde (46 μL, 36 mg, 0.50 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 48 h to yield (*R*)-(−)-**14** (87 mg, 88%) as a pale yellow semisolid. A 92% ee was determined by HPLC analysis (Chiralcel OD column, 50% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C) T_{major} = 9.0 min, T_{minor} = 9.8 min. $[\alpha]^{22}_D$ = −3.68° (*c* = 1.00, $CHCl_3$). R_f = 0.3 (hexanes/EtOAc 5:1). IR (film cast, $CHCl_3$): 3442 (s, broad), 3081 (w), 3064 (w), 2964 (s), 2930 (m), 2873 (m), 2242 (w), 1569 (w), 1025 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.39−7.30 (m, 3H), 4.32 (t, *J* = 5.8 Hz, 1H), 1.96 (app octet, *J* = 6.6 Hz, 1H), 1.86 (d, *J* = 5.9 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 129.4, 128.6, 121.7, 82.5, 78.4, 73.4, 70.4, 68.7, 34.8, 18.2, 17.7. EIMS *m*/*z* 198.1 (M^+, 17), 155.0 ($[M - i\text{-}Pr]^+$, 100). EI HRMS calcd for $C_{14}H_{14}O$ (M^+) 198.1045, found 198.1045.

Compound 15. Compound **11c** (153 mg, 0.601 mmol, 1.2 equiv) was combined with $Zn(OTf)_2$ (298 mg, 0.820 mmol, 1.6 equiv), (−)-*N*-methylephedrine (110 mg, 0.63 mmol, 1.3 equiv), Et_3N (84 μL, 61 mg, 0.60 mmol, 1.2 equiv), and cyclohexanecarboxaldehyde (56 mg, 0.50 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 74 h to yield (*S*)-(+)-**15** (150 mg, 82%) as a pale yellow semisolid. A 97% ee was determined by ^{19}F NMR analysis of the corresponding ester derived from (*R*)-MTPA chloride (−71.89 ppm (major), −72.27 ppm minor)). $[\alpha]^{22}_D$ = 9.49° (*c* = 0.76, $CHCl_3$). R_f = 0.2 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3372 (m), 2927 (s), 2854 (s), 2237 (m), 1603 (s), 1567 (w), 1509 (s), 1251 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 4.30 (t, *J* = 6.0 Hz, 1H), 3.96 (t, *J* = 6.6 Hz, 1H), 1.89 (bd, *J* = 12.7 Hz, 2H), 1.82−1.72 (m, 5H), 1.72−1.56 (m, 2H), 1.49−1.42 (m, 2H), 1.39−1.08 (m, 14H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 134.3, 114.8, 113.3, 82.2, 78.9, 72.2, 70.8, 68.3, 68.0, 44.4, 31.9, 29.5, 29.4, 29.3, 28.7, 28.3, 26.4, 26.1, 26.01, 25.99, 22.8, 14.2. EIMS *m*/*z* 366.3 (M^+, 34), 283.2

([M − C_6H_{11}]$^+$, 64), 55 ($C_4H_7^+$, 100). EI HRMS calcd for $C_{25}H_{34}O_2$ (M^+) 366.2559, found 366.2566.

Compound 16. Compound **11d** (132 mg, 0.709 mmol, 1.1 equiv) was combined with $Zn(OTf)_2$ (406 mg, 1.12 mmol, 1.7 equiv), (−)-*N*-methylephedrine (129 mg, 0.720 mmol, 1.1 equiv), Et_3N (110 μL, 77 mg, 0.76 mmol, 1.2 equiv), and isobutyraldehyde (59 μL, 47 mg, 0.65 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 48 h to yield (*S*)-(+)-**16** (138 mg, 93%) as a pale yellow semisolid. A 98% ee was determined by HPLC analysis (Chiralcel OD column, 5% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C) T_{major} = 42.6 min, T_{minor} = 49.4 min. $[\alpha]^{22}_D$ = 2.46° (*c* = 0.90, $CHCl_3$). R_f = 0.3 (hexanes/EtOAc 5:1). IR (film cast, $CHCl_3$): 3386 (m, broad), 2963 (s), 2933 (m), 2873 (m), 2839 (m), 2237 (m), 1604 (s), 1567 (w), 1510 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 4.31 (d, *J* = 5.7 Hz, 1H), 3.82 (s, 3H), 1.94 (app octet, *J* = 6.4 Hz, 2H), 1.88 (bs, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 134.2, 114.1, 113.4, 81.8, 78.5, 72.1, 70.5, 68.6, 55.3, 34.8, 18.1, 17.6. EIMS *m*/*z* 288.1 (M^+, 37), 185.1 ([M − *i*-Pr]$^+$, 100). EI HRMS calcd for $C_{15}H_{16}O_2$ (M^+) 228.1150, found 228.1153.

Compound 17. Compound **11e** (53 mg, 0.50 mmol, 1.3 equiv) was combined with $Zn(OTf)_2$ (348 mg, 0.957 mmol, 2.5 equiv), (+)-*N*-methylephedrine (132 mg, 0.736 mmol, 1.9 equiv), Et_3N (98 μL, 71 mg, 0.70 mmol, 1.8 equiv), and isobutyraldehyde (35 μL, 28 mg, 0.39 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 60 h to yield (*R*)-(−)-**17** (30 mg, 43%) as a yellow oil. An 88% ee was determined by ^{19}F NMR analysis of the corresponding ester derived from (*R*)-MTPA chloride (−72.34 ppm (major), −71.97 ppm (minor)). $[\alpha]^{22}_D$ = −3.51° (*c* = 0.87, $CHCl_3$). R_f = 0.4 (hexanes/EtOAc 5:1). IR (film cast, $CHCl_3$): 3354 (m, broad), 2961 (s), 2934 (s), 2874 (m), 2254 (m), 1467 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (d, *J* = 5.7 Hz, 1H), 2.29 (dt, *J* = 7.0, 0.9, 2H), 1.95−1.83 (m, 2H), 1.56−1.37 (m, 4H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.4, 75.3, 70.6, 68.3, 64.4, 34.6, 30.2, 21.9, 18.9, 18.0, 17.4, 13.2. EIMS *m*/*z* 178.1 (M^+, 4), 149.1 ([M − Et]$^+$, 6), 135.1 ([M − *i*-Pr]$^+$, 100). EI HRMS calcd for $C_{12}H_{18}O$ (M^+) 178.1358, found 178.1362.

Compound 18. Compound **11f** (92 mg, 0.76 mmol, 1.2 equiv) was combined with $Zn(OTf)_2$ (312 mg, 0.858 mmol, 1.3 equiv), (−)-*N*-methylephedrine (125 mg, 0.700 mmol, 1.1 equiv), Et_3N (110 μL, 77 mg, 0.76 mmol, 1.2 equiv), and isobutyraldehyde (59 μL, 47 mg, 0.65 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 60 h to yield (*S*)-(+)-**18** (87 mg, 65%) as a yellow liquid. An 93% ee was determined by ^{19}F NMR analysis of the corresponding ester derived from (*R*)-MTPA chloride (−71.98 ppm (major), −72.35 ppm minor)). $[\alpha]^{22}_D$ = 4.16° (*c* = 0.25, $CHCl_3$). R_f = 0.4 (hexanes/EtOAc 5:1). IR (film cast, $CHCl_3$): 3361 (m, broad), 2960 (s), 2932 (s), 2872 (m), 2860 (m), 2254 (m) 1028 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (t, *J* = 5.6 Hz, 1H), 2.28 (td, *J* = 7.1, 0.9 Hz, 2H), 1.89 (app octet, *J* = 6.9 Hz, 1H), 1.79 (d, *J* = 5.9 Hz, 1H), 1.53 (quintet, *J* = 7.3 Hz, 2H), 1.42−1.24 (m, 6H), 1.01 (d, *J* = 6.7, Hz, 3H), 0.99 (d, *J* = 6.8, Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.5, 75.3, 70.6, 68.4, 64.4, 34.7, 31.2, 28.5, 28.1, 22.5, 19.3, 18.0, 17.5, 14.0. EIMS *m*/*z* 206.2 (M^+, 2), 191.1 ([M − Me]$^+$, 4), 177.1 ([M − Et]$^+$, 6), 163.1 ([M − *i*-Pr]$^+$, 100). EI HRMS calcd for $C_{14}H_{22}O$ (M^+) 206.1671, found 206.1665.

Compound 19. Compound **11g** (82 mg, 0.55 mmol, 1.2 equiv) was combined with $Zn(OTf)_2$ (210 mg, 0.58 mmol, 1.3 equiv), (−)-*N*-methylephedrine (112 mg, 0.625 mmol, 1.4 equiv), Et_3N (90 μL, 61 mg, 0.60 mmol, 1.3 equiv), and isobutyraldehyde (41 μL, 32 mg, 0.45 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 48 h to yield (*S*)-(+)-**19** (76 mg, 77%) as a yellow oil. A 90% ee was determined by ^{19}F NMR analysis of the corresponding ester derived from (*R*)-MTPA chloride (−71.99 ppm (major), −72.36 ppm (minor)). $[\alpha]^{22}_D$ = 3.74° (*c* = 1.00, $CHCl_3$). R_f = 0.3 (hexanes/EtOAc 5:1). IR (film cast, $CHCl_3$): 3344 (m, broad), 2959 (s), 2930 (s), 2872 (m), 2858 (m), 2254 (m), 1028 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (d, *J* = 5.7 Hz, 1H), 2.27 (t, *J* = 7.0 Hz, 2H), 1.95−1.84 (m, 2H), 1.53 (quintet, *J* = 7.3, 2H), 1.41−1.26 (m, 8H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.7, 75.5, 70.8, 68.5, 64.6, 34.8, 31.8, 29.0, 28.9, 28.3, 22.8, 19.4, 18.2, 17.6, 14.2. EIMS *m*/*z* 220.2 (M^+, 1), 177.1 ([M − *i*-Pr]$^+$, 100). EI HRMS calcd for $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1825.

Compound 20. Compound **11h** (105 mg, 0.510 mmol, 1.3 equiv) was combined with $Zn(OTf)_2$ (338 mg, 0.930 mmol, 2.4 equiv), (−)-*N*-methylephedrine (99 mg, 0.55 mmol, 1.4 equiv), Et_3N (77 μL, 56 mg, 0.55 mmol, 1.4 equiv), and isobutyraldehyde (34 μL, 28 mg, 0.38 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 40 h to yield (*S*)-(+)-**20** (95 mg, 89%) as a yellow oil. A 91% ee was determined by HPLC (Chiralpak AS column, 1% *i*-PrOH in heptane, 0.5 mL/min, λ = 254 nm, column temperature = 2.5 °C) T_{minor} = 20.0 min, T_{major} = 22.5 min. $[\alpha]^{22}_D$ = 2.35° (*c* = 2.00, $CHCl_3$). R_f = 0.5 (hexanes/EtOAc 5:1). IR (film cast, $CHCl_3$): 3314 (m, broad), 2961 (s), 2945 (s), 2867 (s), 2219 (w), 2103 (m), 1464 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (d, *J* = 5.8, 1H), 1.98 (broad singlet, 1H), 1.91 (app octet, *J* = 6.6, 1H), 1.08 (s, 21H), 1.03 (d, *J* = 6.8, 3H) 1.01 (d, *J* = 6.9, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.9, 84.4, 76.5, 70.9, 68.3, 34.6, 18.5, 18.0, 17.6, 11.2. EIMS *m*/*z* 278.2 (M^+, 9), 235.2 ([M − *i*-Pr]$^+$, 100); EIHRMS calcd for $C_{17}H_{30}OSi$ (M^+) 278.2066, found 278.2065.

Compound 21. Compound **12a** (32 mg, 0.16 mmol, 1.1 equiv) was combined with $Zn(OTf)_2$ (210 mg, 0.59 mmol, 4.9 equiv),[34] (−)-*N*-methylephedrine (81 mg, 0.45 mmol, 3.8 equiv), Et_3N (60 μL, 44 mg, 0.43 mmol, 3.6 equiv), and isobutyraldehyde (11 μL, 8.7 mg, 0.12 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 72 h to yield (*S*)-(+)-**21** (23 mg, 69%) as a beige semisolid. An 89% ee was determined by ^{19}F NMR analysis of the corresponding ester derived from (*R*)-MTPA chloride (−71.92 ppm (major), −72.27 ppm minor)). $[\alpha]^{22}_D$ = 11.42° (*c* = 0.50, $CHCl_3$). R_f = 0.5 (hexanes/EtOAc 5:1). IR (film cast, $CHCl_3$): 3359 (m, broad), 3086 (w), 3039 (w), 2964 (s), 2928 (s), 2872 (m), 2191 (m), 2103 (w), 1603 (w), 1503 (w), 1464 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 4.27 (t, *J* = 5.8 Hz, 1H), 1.94 (app octet, *J* = 6.7 Hz, 1H), 1.81 (d, *J* = 5.9 Hz, 1H), 1.31 (s, 9H), 1.04 (d, *J* = 6.7 Hz, 3H) 1.03 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 133.0, 125.7, 117.8, 79.9, 77.7, 73.8, 70.9, 68.6, 65.8, 63.6, 35.2, 34.9, 31.2, 18.2, 17.6. EIMS *m*/*z* 278.2 (M^+, 26), 235.1 ([M − *i*-Pr]$^+$, 100). EI HRMS calcd for $C_{20}H_{22}O$ (M^+) 278.1671, found 278.1674.

Compound 22. Compound **12a** (82 mg, 0.40 mmol, 1.2 equiv) was combined with $Zn(OTf)_2$ (182 mg, 0.501 mmol, 1.4 equiv), (−)-*N*-methylephedrine (81 mg, 0.45 mmol, 1.3 equiv), Et_3N (65 μL, 45 mg, 0.45 mmol, 1.3 equiv), and cyclohexanecarboxaldehyde (42 μL, 39 mg, 0.35 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 90 h to yield (*S*)-(+)-**22** (40 mg, 36%) as a pale yellow oil. A 90% ee was determined by ^{19}F NMR analysis of the corresponding ester derived from (*S*)-MTPA chloride (−72.26 ppm (major), −71.89 ppm (minor)). $[\alpha]^{22}_D$ = 7.56° (*c* = 1.00, $CHCl_3$). R_f = 0.5 (hexanes/EtOAc 5:1). IR (film cast, $CHCl_3$): 3351 (m, broad), 3086 (w), 3038 (w), 2929 (s), 2854 (s), 2189 (m), 2104 (w), 1603 (w), 1503 (w) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 4.27 (t, *J* = 6.0 Hz, 1H), 1.86 (bd, *J* = 12.8 Hz, 2H), 1.80−1.78 (m, 3H), 1.69 (bd, *J* = 12.3 Hz, 1H), 1.65−1.58 (m, 1H), 1.32−1.05 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 132.8, 125.5, 117.7, 80.0, 77.5, 73.6, 70.8, 67.8, 65.4, 63.4, 44.2, 35.0, 31.0, 28.5, 28.1, 26.2, 25.80, 25.77. EIMS *m*/*z* 318.2 (M^+, 61), 303.2 ([M − Me]$^+$, 26), 235.1 ([M − C_6H_{11}]$^+$, 100). EI HRMS calcd for $C_{23}H_{26}O$ (M^+) 318.1984, found 318.1987.

Compound 22 with Hunig's Base (Table 5, entry 7). Compound **12a** (186 mg, 0.90 mmol, 1.2 equiv) was combined with

$Zn(OTf)_2$ (476 mg, 1.31 mmol, 1.4 equiv), (+)-*N*-methylephedrine (160 mg, 0.89 mmol, 1.1 equiv), *i*-Pr_2NEt (171 μL, 127 mg, 0.98 mmol, 1.2 equiv), and cyclohexanecarboxaldehyde (99 μL, 92 mg, 0.82 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 30 h to yield (*R*)-(−)-**22** (136 mg, 52%) as a pale yellow oil. A 94% ee was determined by ^{19}F NMR analysis of the corresponding ester derived from (*S*)-MTPA chloride (−71.89 ppm (major), −72.26 ppm (minor)). $[\alpha]^{22}_D = -7.76°$ (*c* = 1.73, $CHCl_3$). R_f = 0.5 (hexanes/EtOAc 5:1).

Compound 23. Compound **12b** (162 mg, 0.600 mmol, 1.2 equiv) was combined with $Zn(OTf)_2$ (254 mg, 0.699 mmol, 1.4 equiv), (+)-*N*-methylephedrine (108 mg, 0.602 mmol, 1.2 equiv), Et_3N (85 μL, 62 mg, 0.61 mmol, 1.2 equiv), and isobutyraldehyde (46 μL, 36 mg, 0.50 mmol, 1.0 equiv) PhMe (1 mL) as per the general procedure for 61 h to yield (*R*)-(−)-**23** (137 mg, 80%) as a white semisolid that turned purple upon decomposition. A 89% ee was determined by ^1H NMR analysis of the corresponding ester derived from (*R*)-MTPA chloride (−71.95 ppm minor), −72.30 ppm (major)). $[\alpha]^{22}_D = -1.60°$ (*c* = 1.00, $CHCl_3$). R_f = 0.2 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3344 (m, broad), 2959 (s), 2925 (s), 2854 (s), 2218 (m), 1467 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (d, *J* = 5.6 Hz, 1H), 2.30 (t, *J* = 7.0 Hz, 2H), 1.91 (app octet, *J* = 6.6 Hz, 1H), 1.80 (broad singlet, 1H), 1.54 (quintet, *J* = 7.3 Hz, 2H), 1.40−1.27 (m, 22H), 1.01 (t, *J* = 6.8 Hz, 6H), 0.89 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.3, 70.8, 68.4, 65.4, 64.0, 59.0, 34.7, 31.9, 29.7, 29.65, 29.57, 29.49, 29.4, 29.0, 28.2, 28.0, 25.4, 22.7, 19.4, 18.0, 17.4, 14.1 (two signals coincident or not observed). EIMS *m*/*z* 342.3 (M^+, 2), 327.3 ($[M - Me]^+$, 7), 299.2 ($[M - i\text{-}Pr]^+$, 100). EI HRMS calcd for $C_{24}H_{38}O$ (M^+) 342.2923, found 342.2919.

Compound (*R*)-(−)-24 (Table 4, entry 4). Compound **12c** (120 mg, 0.52 mmol, 1.2 equiv) was combined with $Zn(OTf)_2$ (260 mg, 0.72 mmol, 1.6 equiv), (+)-*N*-methylephedrine (108 mg, 0.602 mmol, 1.3 equiv), Et_3N (80 μL, 0.57 mmol, 1.3 equiv), and isobutyraldehyde (41 μL, 32 mg, 0.45 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 35 h to yield (*R*)-(−)-**24** (106 mg, 78%) as a yellow semisolid. $[\alpha]^{22}_D = -2.64°$ (*c* =1.00, $CHCl_3$). Determination of enantiomeric excess by HPLC analysis and Mosher ester formation was unsuccessful.

The other enantiomer, (*S*)-(+)-**24** (Table 4, entry 5), was synthesized from **12c** (120 mg, 0.52 mmol, 1.2 equiv), $Zn(OTf)_2$ (260 mg, 0.72 mmol, 1.6 equiv), (−)-*N*-methylephedrine (101 mg, 0.563 mmol, 1.3 equiv), Et_3N (38 μL, 53 mg, 0.52 mmol, 1.2 equiv), and isobutyraldehyde (40 μL, 31 mg, 0.44 mmol, 1.0 equiv) in PhMe (1 mL) as per the general procedure for 36 h to yield (*S*)-(+)-**24** (108 mg, 81%) as a yellow semisolid. Determination of enantiomeric excess by HPLC analysis and Mosher ester formation was unsuccessful.

Data for (*S*)-(+)-**24**: $[\alpha]^{22}_D = 1.86°$ (*c* = 0.29, $CHCl_3$). R_f = 0.4 (hexanes/EtOAc 5:1). IR (film cast, $CHCl_3$): 3328 (m, broad), 2961 (s), 2945 (s), 2892 (m), 2867 (s), 2163 (w), 2077 (m), 1463 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (t, *J* = 4.4 Hz, 1H), 1.98 (d, *J* = 3.9 Hz, 1H), 1.91 (app octet, *J* = 6.6 Hz, 1H), 1.08 (s, 21H), 1.00 (dd, *J* = 6.8, 8.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 89.5, 85.3, 77.9, 70.5, 68.3, 63.9, 60.1, 34.7, 18.5, 18.0, 17.4, 11.2. EIMS *m*/*z* 302.2 (M^+, 2), 259.2 ($[M - i\text{-}Pr]^+$, 100). EI HRMS calcd for $C_{19}H_{30}OSi$ (M^+) 302.2066, found 302.2057.

Compound 25a. Compound (*S*)-(+)-**20** (13 mg, 0.047 mmol), benzyl azide (6.0 mg, 0.045 mmol), $CuSO_4 \cdot 5H_2O$ (100 mg, 0.4 mmol), ascorbic acid (100 mg, 0.6 mmol), and H_2O (0.5 mL) were reacted in DMF (3 mL) as per the general procedure, and the reaction was quenched after 30 min. Column chromatography (silica gel, CH_2Cl_2) afforded (*S*)-(−)-**25a** (6.0 mg, 51%) as a slightly off-white solid. $[\alpha]^{22}_D = -1.68°$ (*c* = 0.500, $CHCl_3$). A 91% ee was determined by HPLC analysis (Chiracel OD column, 10% *i*-PrOH/hexanes, 0.5 mL/min, λ= 254, column temperature = 25 °C) T_{minor} 74.5 min, T_{major} 82.2 min.

The racemic triazole *rac*-**25a** was synthesized from *rac*-**20** (3.0 mg, 0.011 mmol), benzyl azide (3.0 mg, 0.023 mmol), $CuSO_4 \cdot 5H_2O$ (100 mg, 0.4 mmol), ascorbic acid (100 mg, 0.6 mmol), and H_2O (0.5 mL) reacted in DMF (3 mL) via the general procedure, and the reaction was quenched after 30 min. Column chromatography (silica gel, CH_2Cl_2) afforded *rac*-**25a** (1.5 mg, 53%), which was used for determining HPLC conditions to calculate the enantiomeric excess.

Data for (*S*)-(−)-**25a**. R_f = 0.4 (hexanes/EtOAc 1:1). IR (film cast, $CHCl_3$): 3362 (m, broad), 3140 (m), 3066 (w), 3034 (w), 2962 (s), 2927 (s), 2872 (s), 1458 (s), 1054 (s) cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.40−7.37 (m, 3H), 7.27−7.25 (m, 2H), 5.52 (s, 2H), 4.37 (d, *J* = 5.6 Hz, 1H), 1.99−1.92 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 134.0, 130.9, 129.2, 129.0, 128.1, 125.9, 92.7, 75.0, 68.3, 54.3, 34.4, 18.1, 17.6. EIMS *m*/*z* 255.1 (M^+, 4), 237.1 ($[M - H_2O]^+$, 6), 212.1 ($[M - CH_3N_2]^+$, 25), 184.1 ($[M - i\text{-}Pr - N_2]^+$, 37), 91.1 ($[C_7H_7]^+$, 100). EI HRMS calcd for $C_{15}H_{17}N_3O$ 255.1372, found 255.1366.

Compound 25b. Compound (*S*)-(+)-**24** (13 mg, 0.043 mmol), benzyl azide (5.7 mg, 0.043 mmol), $CuSO_4 \cdot 5H_2O$ (100 mg, 0.4 mmol), ascorbic acid (100 mg, 0.6 mmol), and H_2O (0.5 mL) were reacted in DMF (3 mL) as per the general procedure, and the reaction was quenched after 40 min. Column chromatography (silica gel, hexanes/EtOAc, 3:1) afforded (*S*)-(−)-**25b** (7.8 mg, 65%) as a yellow liquid. $[\alpha]^{22}_D = -13.00°$ (*c* = 0.13, $CHCl_3$). A 98% ee was determined by HPLC analysis (Chiralcel OD column, 40% *i*-PrOH/hexanes, 0.5 mL/min, λ = 254, column temperature = 25 °C) T_{major} 18.8 min, T_{minor} 21.4 min with (*S*)-(−)-**25b**.

The other enantiomer (*R*)-(+)-**25b** was synthesized from (*R*)-(−)-**24** (13 mg, 0.043 mmol), benzyl azide (5.3 mg, 0.040 mmol), $CuSO_4 \cdot 5H_2O$ (100 mg, 0.4 mmol), ascorbic acid (100 mg, 0.6 mmol), and H_2O (0.5 mL) in DMF (3 mL) as per the general procedure, and the reaction was quenched after 40 min. Column chromatography (silica gel, hexanes/EtOAc, 3:1) afforded (*R*)-(+)-**25b** (7.8 mg, 65%) as a yellow liquid. $[\alpha]^{22}_D = 2.67°$ (*c* = 0.06, $CHCl_3$). A 94% ee for (*R*)-(+)-**25b** was determined using the conditions outlined above for (*S*)-(−)-**25b**.

Data for (*R*)-(+)-**25b**: R_f = 0.5 (hexanes/EtOAc 1:1). IR (film cast, $CHCl_3$): 3362 (m, broad), 3141 (m), 3067 (w), 3034 (w), 2963 (s), 2930 (m), 2873 (m), 2243 (w), 1457 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.40−7.38 (m, 3H), 7.28−7.25 (m, 2H), 5.53 (s, 2H), 4.30 (d, *J* = 5.6, 1H), 1.93 (app octet, *J* = 5.6 Hz, 1H), 1.75 (broad singlet, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 133.8, 130.2, 129.3, 129.1, 128.2, 127.4, 83.6, 76.9, 69.6, 68.4, 67.1, 54.4, 34.6, 18.0, 17.4. ESI HRMS calcd for $C_{17}H_{17}N_3O_2Na$ ($[M + Na]^+$) 302.1264, found 302.1262; calcd for $C_{17}H_{18}N_3O_2$ ($[M + H]^+$) 280.1444, found 280.1446.

■ ASSOCIATED CONTENT

Supporting Information. Additional synthetic and spectroscopic data for optimization experiments, HPLC traces for determination of enantiomeric excess, NMR spectra for Mosher ester analysis, and crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Pan, Y.; Lowary, T. L.; Tykwinski, R. R. *Can. J. Chem.* **2009**, *87*, 1565–1582. (b) Gung, B. W. *C. R. Chim.* **2009**, *12*, 489–505. (c) Minto, R. E.; Blacklock, B. J. *Prog. Lipid Res.* **2008**, *47*, 233–306. (d) Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1034–1057. (e) Bohlmann, F.; Burkhardt, H.; Zdero, C. *Naturally Occurring Acetylenes*; Academic Press: New York, 1973.

(2) Dembitsky, V. M. *Lipids* **2006**, *41*, 883–924.

(3) Hansen, L.; Boll, P. M. *Phytochemistry* **1986**, *25*, 285–293.

(4) (a) Lechner, D.; Stavri, M.; Oluwatuyi, M.; Pereda-Miranda, R.; Gibbons, S. *Phytochemistry* **2004**, *65*, 331–335. (b) Matsunaga, H.; Saita, T.; Nagumo, F.; Mori, M.; Katano, M. *Cancer Chemother. Pharmacol.* **1995**, *35*, 291–296.

(5) Uwai, K.; Oshima, Y.; Sugihara, T.; Ohta, T. *Tetrahedron* **1999**, *55*, 9469–9480.

(6) Lewis, M. D.; Menes, R. *Tetrahedron Lett.* **1987**, *28*, 5129–5132.

(7) Wright, J. J.; Puar, M. S.; Pramanik, B.; Fishman, A. *J. Chem. Soc., Chem. Commun.* **1988**, 413–414.

(8) Patel, M.; Conover, M.; Horan, A.; Loebenberg, D.; Marquez, J.; Mierzwa, R.; Paur, M. S.; Yarborough, R.; Waitz, J. A. *J. Antibiot.* **1988**, *41*, 794–797.

(9) For isolation, see: Marles, R. J.; Farnsworth, N. R.; Neill, D. A. *J. Nat. Prod.* **1989**, *52*, 261–266. For determination of absolute configuration, see: Rasmussen, H. B.; Christensen, S. B.; Kvist, L. P.; Kharazmi, A.; Huansi, A. G. *J. Nat. Prod.* **2000**, *63*, 1295–1296.

(10) Ito, A.; Cui, B. L.; Chavez, D.; Chai, H. B.; Shin, Y. G.; Kawanishi, K.; Kardono, L. B. S.; Riswan, S.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2001**, *64*, 246–248.

(11) Rashid, M. A.; Gustafson, K. R.; Cardellina, J. H., II; Boyd, M. R. *Nat. Prod. Lett.* **2001**, *15*, 21–26.

(12) (a) Rücker, G.; Kehrbaum, S.; Sakulas, H.; Lawong, B.; Goeltenboth, F. *Planta Med.* **1992**, *58*, 266–269. (b) Tobinaga, S.; Sharma, M. K.; Aalbersberg, W. G. L.; Watanabe, K.; Iguchi, K.; Narui, K.; Sasatsu, M.; Waki, S. *Planta Med.* **2009**, *75*, 624–628.

(13) For reviews, see: (a) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983. (b) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886. (c) Cozzi, P. G.; Hilgraf, R.; Zimmerman, N. *Eur. J. Org. Chem.* **2004**, 4095–4105.

(14) Ashwanden, P.; Carreira, E. M. Addition of Terminal Acetylides to C═O and C═N Electrophiles. In *Acetylene Chemistry. Chemistry, Biology and Material Science*; Diederich, F.; Stang, P. J.; Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005; pp 101−138.

(15) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245–11246. (b) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807. (c) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373–381.

(16) When non α- or β-branched aldehydes were used, the enantioselectivities were lower, 70−88% ee, see ref 15b. When unsaturated aldehydes were used, a competing Cannizaro reaction resulted in lower than desirable yields, see ref 13a.

(17) (a) Chen, Z.; Xiong, W.; Jiang, B. *Chem. Commun.* **2002**, 2098–2099. (b) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451–3453. (c) Jiang, B.; Feng, Y. *Tetrahedron Lett.* **2002**, *43*, 2975–2977. (d) Jiang, B.; Si, Y.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 216–218. (e) Kamble, R. M.; Singh, V. K. *Tetrahedron Lett.* **2003**, *44*, 5347–5349.

(18) Prior to Trost's recent work in ref 19, only a single example of asymmetric addition of a diyne into an aldehyde had been reported, using Carreira's protocol toward the synthesis of the natural products strongylodiols A and B, see: Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813–6817.

(19) Trost, B.; Chan, V. S.; Yamamoto, D. *J. Am. Chem. Soc.* **2010**, *132*, 5186–5192.

(20) (a) Fritsch, P. *Liebigs Ann. Chem.* **1894**, *279*, 319–323. (b) Buttenberg, W. P. *Liebigs Ann. Chem.* **1894**, *279*, 324–337. (c) Wiechell, H. *Liebigs Ann. Chem.* **1894**, *279*, 337–344.

(21) For reviews, see: (a) Jahnke, E.; Tykwinski, R. R. *Chem. Commun.* **2010**, *46*, 3235–3249. (b) Chalifoux, W. A.; Tykwinski, R. R. *Chem. Rec.* **2006**, *6*, 169–182. (c) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795–3849. (d) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383–405.

(22) For examples, see: (a) Bichler, P.; Chalifoux, W. A.; Eisler, S.; Shi Shun, A. L. K.; Chernick, E. T.; Tykwinski, R. R. *Org. Lett.* **2009**, *11*, 519–522. (b) Eisler, S.; Chahal, N.; McDonald, R.; Tykwinski, R. R. *Chem.—Eur. J.* **2003**, *9*, 2542–2550. (c) Shi Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 1339–1347. (d) Shi Shun, A. L. K.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 6810–6813. (e) Eisler, S.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2000**, *122*, 10736–10737.

(23) Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45–56.

(24) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747.

(25) The Flack parameter value obtained was −0.1(9); see Supporting Information.

(26) See, for example, ref 18.

(27) Luu, T.; Tykwinski, R. R. *J. Org. Chem.* **2006**, *71*, 8982–8985.

(28) For the trapping of polyynes with benzyl azide via CuAAC, see: (a) Luu, T.; Medeos, B.; Graham, E.; Vallee, D.; McDonald, R.; Ferguson, M. J.; Tykwinski, R. R. *J. Org. Chem.* **2010**, *75*, 8498–8507. (b) Luu, T.; McDonald, R.; Tykwinski, R. R. *Org. Lett.* **2006**, *8*, 6035–6038.

(29) For selected reviews, see: (a) Huisgen, R. In *1,3−Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 1−176. (b) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302–1315. (c) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207–4220. (d) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015.

(30) Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 964–971.

(31) Made from the dibromoolefin (ref 28a) as per the general procedure reported in ref 22c.

(32) (a) Jiang, H.-F.; Wang, A.-Z. *Synthesis* **2007**, 1649–1654. (b) Dabdoub, M. J.; Dabdoub, V. B.; Lenardão, E. J. *Tetrahedron Lett.* **2001**, *42*, 1807–1809.

(33) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. (c) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *33*, 2143–2147.

(34) An excess of reagents were inadvertently used in this case, discovered only after the conclusion of the project.