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Asymmetric Synthesis of Propargylic α-Stereogenic Tertiary Amines by Reductive Alkynylation of Tertiary Amides Using Ir/Cu Tandem Catalysis

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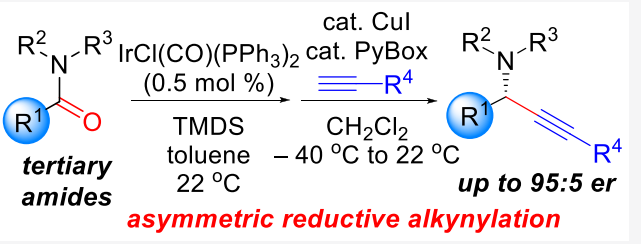
ABSTRACT: The development of an asymmetric protocol for the reductive alkynylation of amides to access important α-stereogenic tertiary propargylic amines is reported using a tandem Ir-catalyzed hydrosilylation/enantioselective Cu-catalyzed alkynylation. The reaction utilizes a Cu/PyBox catalyst system in the alkynylation step to achieve asymmetry and affords excellent yields with moderate to good levels of enantiocontrol while employing low Ir-catalyst loadings (0.5 mol %).



Chiral α-stereogenic amines are prevalent motifs found in organic compounds and drug molecules leading to important biological activity.[1] As a result, synthetic methods for the stereoselective preparation of α-stereogenic amines is an important endeavor in organic chemistry.[2] One powerful emerging strategy for the synthesis of α-stereogenic amines utilizes amides as building blocks through partial reduction[3] or activation[4,5] of the amide followed by reaction with nucleophiles (Figure 1A,B) in an overall deoxygenative process.[6] The value of this approach arguably lies in the reliable access to amide building blocks **3** from ubiquitous carboxylic acid (**1**) and amine (**2**) precursors[7] enabling a programmatic technique for the preparation of α-stereogenic amines **4**. Such protocols are enabled by the conversion of amide **3** to an electrophilic *N,O*-aminal derivative (**5**,**6**) that is subsequently functionalized with nucleophiles (Figure 1B).[3−6,8,9] Conversion of the amide into the requisite electrophilic species is achieved through either amide activation,[4,5] typically employing Tf_2O, followed by trapping with an organometallic reagent to afford **5** or through partial reduction of the amide employing the Schwartz reagent (Cp_2ZrHCl),[3g] DIBAL,[3h] or by Ir-[3a−f] or Mo-catalyzed[3i,j] hydrosilylation to give **6**. Of these methods, reductive functionalization of tertiary amides through partial reduction by Ir-catalyzed hydrosilylation[8] followed by nucleophile trapping has been proven to be an attractive technique for the synthesis of α-stereogenic tertiary amines due to the robustness of the Ir-catalyzed hydrosilylation reaction that occurs at very low Ir-catalyst loading.[6,8] However, the majority of these processes produce racemic α-stereogenic amines and enantioselective variants are extremely rare.[9] As a result, our group became interested in developing catalytic asymmetric variants of these processes to access α-stereogenic amines in an enantioenriched form through coupling processes employing partially reduced amides from Ir-catalyzed hydrosilylation as electrophiles. Furthermore, because of the reliable nature at which the amide functional group can be prepared synthetically,[7] we reasoned such an asymmetric functionalization of amides would be a highly reliable technique to access α-stereogenic tertiary amines. Based on the elegant work of Huang[3c] where racemic α-stereogenic propargylic tertiary amines were prepared through tandem Ir-catalyzed amide hydrosilylation followed by Cu-catalyzed alkynylation under ligandless conditions, we chose this reaction as an initial starting point to study by investigating the addition of chiral ligands to the reaction to determine if enantioselective ligand-accelerated catalysis[10] could be achieved to afford the α-stereogenic propargylic tertiary amine products in high enantioselectivities (Figure 1C). Furthermore, α-stereogenic propargylic amines are versatile building blocks for complex molecule[11] synthesis that have previously been accessed in an enantioselective fashion through propargylic substitution,[12] the alkynylation of imines,[13] or the aldehyde−amine−alkyne (A^3)[14] coupling reaction. During the course our investigations, Huang and Wang[9b] reported a Cu/bis(phosphine)-catalyzed version of this reaction providing products with high levels of enantiocontrol. This report prompted us to disclose our investigations into the analogous reaction where we have focused on application of chiral PyBox ligands to achieve enantiocontrol. Herein, we report[15] our findings on the

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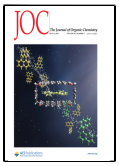

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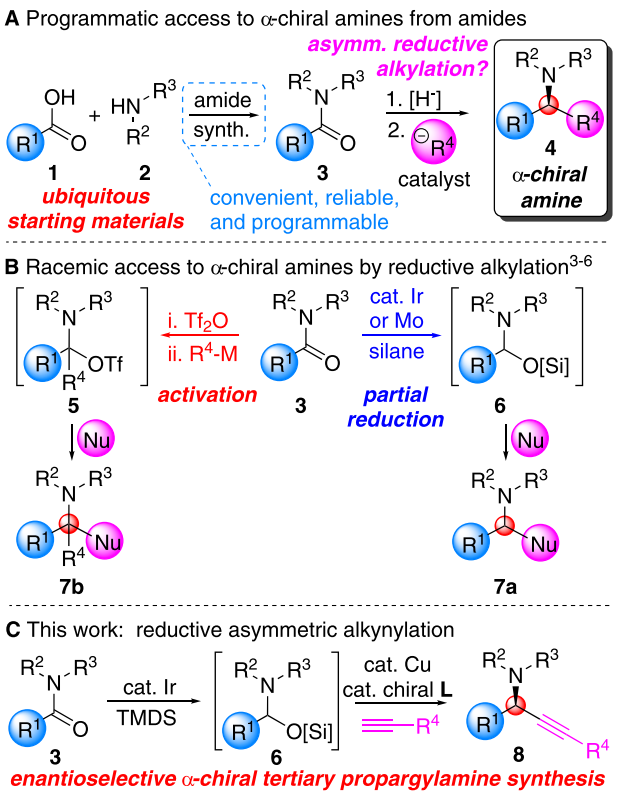
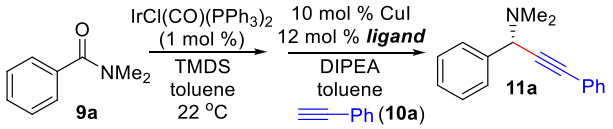


Figure 1. Preparation of α-stereogenic amines through reductive alkylation of amides.

development of an enantioselective α-stereogenic propargylic amine synthesis through tandem partial amide reduction by Ir-catalyzed hydrosilylation followed by asymmetric Cu/PyBox catalyzed alkynylation.

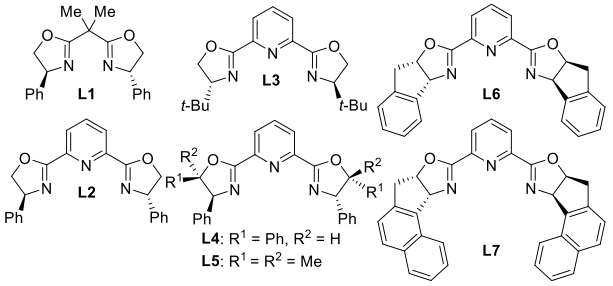
Initial investigation into the feasibility of an asymmetric tandem reductive amide alkynylation reaction was carried out using *N,N*-dimethylbenzamide (**9a**) in an Ir-catalyzed hydrosilylation reaction followed immediately by Cu-catalyzed coupling with phenylacetylene (**10a**) to afford α-stereogenic propargylic amine **11a** (Table 1). Use of chiral Ph-Box ligand **L1** discouragingly afforded product **11a** as a racemate (entry 2). As a result, a series of PyBox ligands (**L2**–**L7**) were next investigated under the hypothesis that the added chelation available with these ligands may enable a more selective catalyst (entries 3–11). Indeed, use of PyBox **L2** afforded nonracemic **11a**, albeit with poor enantioselectivity, and ligand-accelerated catalysis was observed relative to the reaction in the absence of ligand by monitoring the reaction progress throughout the alkynylation step using ^{1}HNMR spectroscopic analysis while performing the reactions in toluene-d_8 (entry 3 vs 1). The reaction employing ligand **L2** (entry 3) was complete in 1 h, whereas the ligandless reaction (entry 1) required >4 h to reach completion. Increasing the steric size of the substituents at the stereogenic centers of the PyBox ligand (i.e., **L3**), and reducing the reaction temperature, did not afford significant improvements in enantioinduction (entry 4). However, it was found that substitution on the *C*-atom of the C–O group of the oxazoline ring of the PyBox ligand (i.e., **L4**–**L7** vs **L2**–**L3**) allowed for significant improvements in enantiocontrol (entries 3 and 4 vs entries 5–11).[16] Performing the reaction at −40 °C was found to be optimal[17] and led to improved stereocontrol relative to

Table 1. Chiral Ligand Survey[a]



entry	ligand	conditions[b]	% yield[c]	er[d]
1[e]	none	22 °C, 6 h	90	50:50
2	**L1**	22 °C, 1 h	91	50:50
3[e]	**L2**	22 °C, 1 h	95	42:58
4	**L3**	−40 to +22 °C[f]	80	62:38
5	**L4**	22 °C, 20 h	89	40:60
6	**L4**	− 40 to +22 °C[f]	94	16:84
7	**L5**	22 °C, 20 h	82	45:55
8	**L6**	−40 to +22 °C[f]	92	86:14
9[g]	**L6**	−40 to +22 °C[f]	92	88:12
10[g,h]	**L6**	−40 to +22 °C[f]	81	92:8
11[g,h]	**L7**	−40 to +22 °C[f]	81	89:11

[a]Conditions: **9a** (0.100 mmol), $IrCl(CO)(PPh_3)_2$ (1 mol %), TMDS (0.20 mmol) in 0.25 mL of toluene, 22 °C, 1 h; CuI (10 mol %), ligand (12 mol %), DIPEA (0.15 mmol), **10a** (0.15 mmol) in 0.50 mL of solvent. [b]Alkynylation conditions. [c]Isolated yield. [d]Value determined by chiral HPLC analysis. [e]Performed in toluene-d_8. [f]Performed at −40 °C for 5 h then allowed to warm to 22 °C and stir overnight. [g]CH_2Cl_2 added in the alkynylation step. [h]Reaction performed in the absence of DIPEA using 5 mol % CuI and 7 mol % ligand.



reactions performed at 22 °C (entry 5 vs 6). Ultimately, aminoindanol-derived PyBox ligand **L6** afforded the highest levels of enantiocontrol (entries 8–10). Dichloromethane (entries 9 and 10) was identified as the optimal reaction solvent,[17] which may be due to the fact that **L6** was found to have poor solubility in most organic solvents except for CH_2Cl_2. Additionally, no exogenous amine base was needed in the alkynylation reaction, and the Cu-catalyst loading could be reduced to 5 mol % with a slight reduction in yield, but with improved stereoselectivity (entry 10). Finally, extending the π-system of the PyBox ligand as in **L7** did not lead to any further improvements (entry 11).

After having identified optimal conditions for the tandem reductive amide alkynylation reaction (Table 1, entry 10), the substrate scope of this process was next investigated (Scheme 1). Varying the R^1-substituent of amide **9** employing phenylacetylene (**10a**) generally afforded similar results (**11a**–**h**). A small electronic effect may be observed where electron-rich aromatic R^1 groups afforded slightly higher levels of enantiocontrol relative to electron-poor aromatics (**11c,d** vs **11e**–**h**). Reduction in the steric size of the R^1 group led to a decrease in enantioselectivity (**11i**). Varying the R^4 group of the alkyne nucleophile (**10**) showed a dramatic effect on enantioselectivity (**11j**–**x**). Alkynes bearing aromatic R^4 groups (**10j**–**q**) generally gave similar levels of enantiocontrol, and

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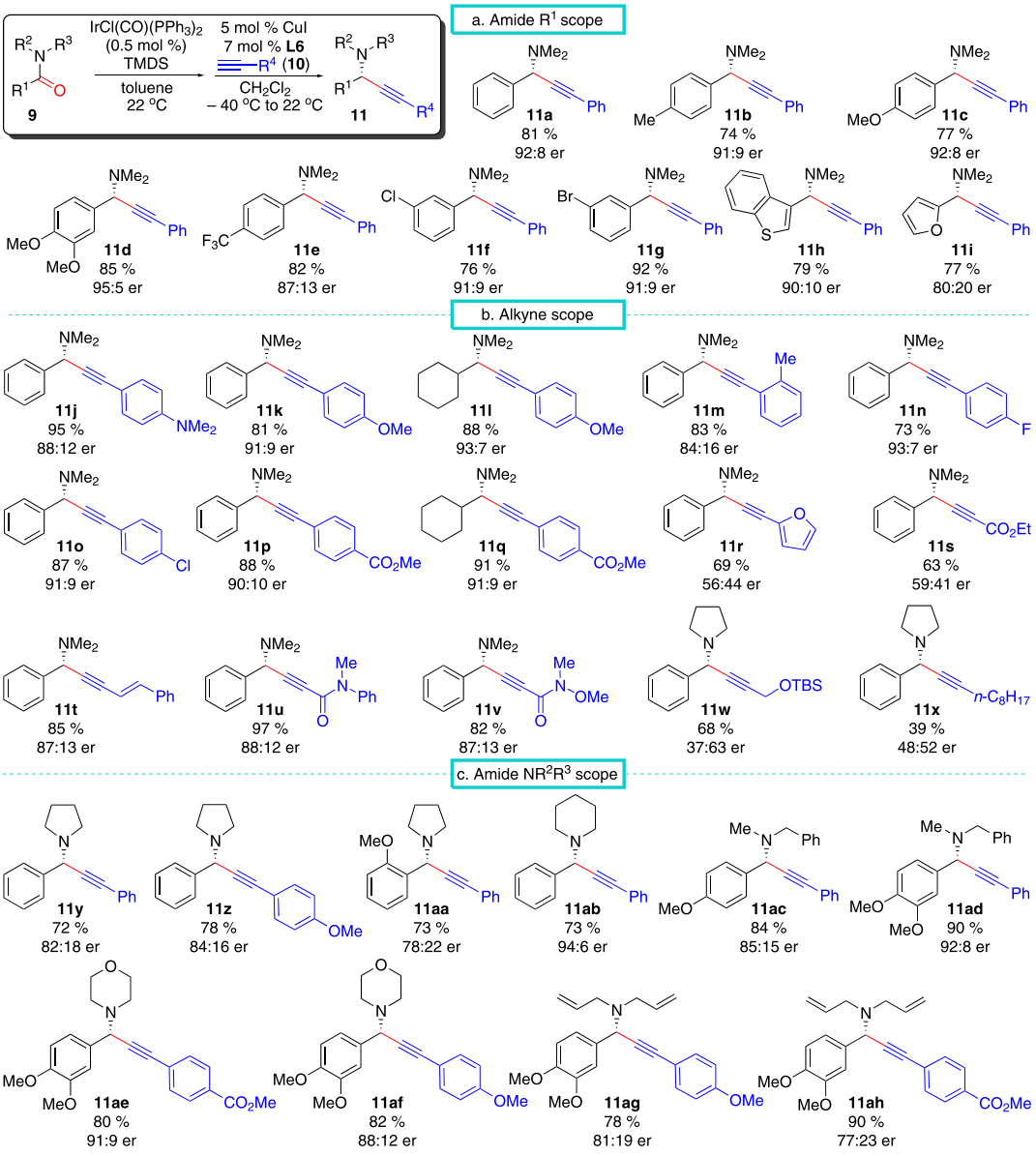
Scheme 1. Scope of the Tandem Reductive Amide Asymmetric Alkynylation Reaction[a]



[a]Reaction utilizes 0.400 mmol of amide **9**; see the Experimental Section.

amides bearing aliphatic R^1 groups could also be used (**11l,q**). However, when the R^4 group of the alkyne was a smaller aromatic ring (**10r**), an ester moiety (**10s**), or an aliphatic group (**10w,x**) very low levels of enantioinduction were obtained. Interestingly, when using a conjugated aromatic group on the alkyne (**10t**) or amide groups (**10u,v**), levels of enantiocontrol similar to that obtained with aromatic alkynes were restored. Finally, analysis of the NR^2R^3 group of amide **9** demonstrated that cyclic (**11y−ab**, **11ae**, **11af**) and acyclic (**11ac**, **11ad**, **11ag**, **11ah**) amino groups were tolerated with similar levels of enantiocontrol. Six-membered carbocyclic amines (**11ab**) afforded improved stereoselectivity relative to smaller five-membered versions (**11y**). Acyclic amino groups larger than CH_3 generally afforded reduced levels of enantiocontrol (**11ac**, **11ad**, **11ag**, **11ah**).

The tandem Ir-catalyzed amide reduction/enantioselective Cu-catalyzed alkynylation reaction could easily be performed on a 1.0 mmol scale with reduction in the Cu catalyst loading to 2 mol % providing near quantitative yield of **11a** in 92.7:7.3 er (Scheme 2a). Furthermore, the synthetic utility of chiral propargylic amines in organic synthesis has already been extensively demonstrated.[11−14] For example, the stereodefined alkenes **12** and **13** could be prepared through application of a recently described Ti-catalyzed hydroalumination reaction[18] (Scheme 2b). Additionally, conversion of α-stereogenic propargylic amines to chiral internal allenes with complete chirality transfer using $AgNO_3$ has already been described elsewhere.[19]

In conclusion, an asymmetric reductive alkynylation of amides using tandem Ir and Cu catalysis for the synthesis of α-stereogenic tertiary propargylic amines was described. Moderate to good enantioselectivities were observed using an aminoindanol-derived PyBox ligand when employing alkynamides or aromatic-substituted alkynes as the coupling partner in the alkynylation step.

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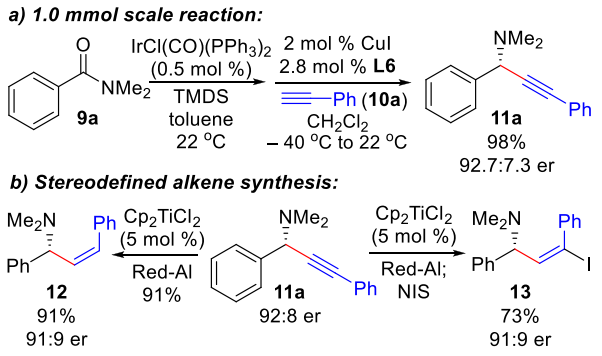
Scheme 2. Practicality of the Amide Reductive Alkynylation Method



EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were recorded on Bruker 600 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Bruker 600 MHz (151 MHz) instrument with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). Chiral HPLC analyses were performed on a Shimadzu Prominence i-series LC-2030C using chiral Daicel columns purchased from Chiral Technologies, Inc. Liquid chromatography was performed using forced flow (flash chromatography) on silica gel purchased from Silicycle. Thin-layer chromatography (TLC) was performed on glass-backed 250 μm silica gel F_{254} plates purchased from Silicycle. Visualization was achieved by using UV light or potassium permanganate in water followed by heating. HRMS was collected using a JEOL AccuTOF-DART mass spectrometer using DART source ionization. All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon with magnetic stirring unless otherwise noted. Solvents were obtained from VWR as HPLC grade and transferred to septa-sealed bottles, degassed by argon sparge, and analyzed by Karl Fischer titration to ensure water content was ≤500 ppm. TMDS (1,1,3,3-tetramethyldisiloxane) was purchased from Alfa Aesar and used as received. Acids and amines were purchased from Sigma-Aldrich, Combi-Blocks, TCI America, Alfa Aesar, or Oakwood Chemicals and used as received. All other materials were purchased from VWR, Sigma-Aldrich, Combi-Blocks, Alfa Aesar, or Strem Chemical Co. and used as received. Ethynyl furan,[20] *N*-methyl-*N*-phenylpropiolamide,[21] and *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane[22] were prepared according to known procedures. Ligands were obtained from commercial vendors or prepared according to the literature (**L4**,[23] **L5**,[24] and **L6**[25]).

General Procedure for the Tandem Ir-/Cu-Catalyzed Alkynylation Reaction (Scheme 1). A 2-dram vial was charged with amide **9** (0.400 mmol) and Vaska's complex (1.5 mg, 0.0020 mmol), and the vial was sealed with a septum. It was then evacuated and backfilled with nitrogen 3 times. Toluene (1 mL) was then charged followed by TMDS (0.14 mL, 0.80 mmol), and the reaction was allowed to stir at room temperature for 1 h. A separate crimp-cap vial was charged with CuI (3.8 mg, 0.020 mmol) and ligand (11.0 mg, 0.028 mmol), and the vial was sealed. It was evacuated and backfilled with nitrogen 3 times and charged with CH_2Cl_2 (3 mL), and the solution was allowed to stir for 15 min at rt. The solution of partially reduced amide from the first vial was then transferred via syringe to the catalyst solution. The reaction was then cooled to −40 °C (dry ice/MeCN), alkyne **10** (0.600 mmol) was added, and stirring was continued at −40 °C for 5 h. The reaction was then allowed to slowly warm to room temperature (22 °C), and stirring was continued overnight. Aqueous NH_4OH (29 wt %, 3 mL) was then added to the reaction, and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography using hexanes/EtOAc or CH_2Cl_2/EtOAc mixtures.

Reaction Performed on 1.0 mmol Scale of 9a. A crimp-cap vial was charged with *N*,*N*-dimethylbenzamide **9a** (149 mg, 1.00 mmol) and Vaska's complex (3.9 mg, 5.0 μmol), and the vial was sealed. It was then evacuated and backfilled with nitrogen 3 times. Toluene (1.0 mL) was then charged followed by TMDS (0.35 mL, 2.0 mmol), and the reaction was allowed to stir at room temperature for 1 h. A 50 mL 3-neck round-bottom flask was charged with CuI (3.8 mg, 0.020 mmol) and ligand (11.0 mg, 0.028.0 mmol). The flask was then evacuated and backfilled with nitrogen 3 times and charged with CH_2Cl_2 (1.5 mL), and the solution was allowed to stir for 15 min. The solution of partially reduced amide from the vial was then transferred via syringe to the catalyst solution. The vial was then rinsed with CH_2Cl_2 (1.5 mL), and the solvent was transferred to the round-bottom flask. The reaction was then cooled to −40 °C (dry ice/MeCN), phenylacetylene (0.16 mL, 1.5 mmol) was added, and stirring was continued at −40 °C for 5 h. The reaction was then allowed to warm to room temperature (22 °C), and stirring was continued overnight. Aqueous NH_4OH (29 wt %, 4 mL), water (2 mL), and additional CH_2Cl_2 (3 mL) were then added to the reaction. After separation of the layers, the aqueous layer was further extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (gradient, hexanes to 25% EtOAc/hexanes) to provide 231 mg (98%) of **11a** as a colorless liquid as a 92.7:7.3 mixture of enantiomers by chiral HPLC: AD-3 × 250 mm, heptane/isopropanol = 98/2, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 4.43 min (major), 4.84 min (minor). Spectral data was in agreement with the literature.[26]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00131.

Additional reaction optimization data, characterization data of all new compounds, chiral HPLC chromatograms and copies of ^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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