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Catalytic Asymmetric Mannich Reaction of α-Fluoronitriles with Ketimines: Enantioselective and Diastereodivergent Construction of Vicinal Tetrasubstituted Stereocenters

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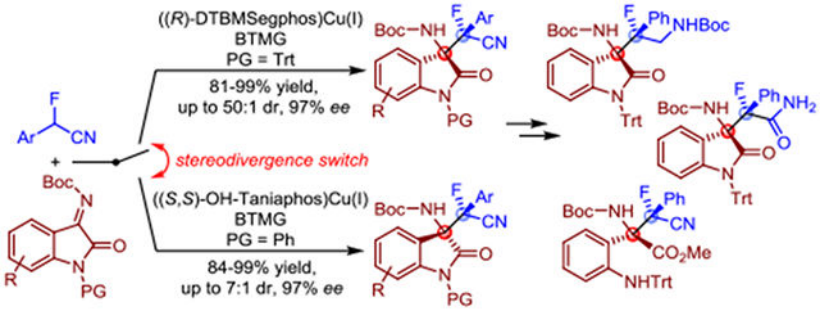
Abstract

Diastereodivergent and enantioselective conversion of isatin ketimines to α-fluoro-β-aminonitriles with vicinal tetrasubstituted stereocenters is achieved by a chiral copper complex/guanidine base catalyzed Mannich reaction with proper choice of the bisphosphine ligand. The reaction is broad in scope, scalable, and provides efficient access to a series of 3-aminoindolinones exhibiting a quaternary carbon-fluorine stereocenter with high yields and stereoselectivities. Selective transformations of the Mannich reaction products into multifunctional 3-aminooxindoles without erosion of enantiomeric and diastereomeric purity highlight the synthetic utility.

Graphical Abstract



Two vicinal tetrasubstituted stereocenters • high yields • high enantio- and diastereoselectivities scalable • practical stereodivergence

Keywords

Enantioselective catalysis; stereodivergence; Mannich reaction; organofluorines; α-fluoro-β-aminonitriles

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Supporting Information.

Experimental details, characterization data including NMR spectra and HPLC chromatograms. The Supporting Information is available free of charge on the ACS Publications website.

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Catalytic enantioselective reactions that produce multifunctional building blocks with carbon-fluorine quaternary stereocenters are of great interest due to the prevalence of this motif in biologically active compounds.[1] In many cases, the *in situ* generation of fluorinated nucleophiles requires the presence of a proximate carbonyl group which substantially limits the pool of substrates that can be applied in catalytic asymmetric synthesis of organofluorines displaying a quaternary chirality center.[2] The use of α-fluorinated nitriles devoid of an activating carbonyl moiety remains very challenging because of the inherent fluxionality of α-metalated nitriles and the low C-H acidity, which complicates catalytic formation of α-cyano carbanions under mild reaction conditions.[3] To the best of our knowledge, stereodivergent catalytic asymmetric additions with α-fluoro-α-arylnitriles have not been reported to date despite the synthetic potential of these prenucleophiles for the construction of chemically versatile scaffolds around a tetrasubstituted carbon-fluorine stereocenter.

Mannich reactions with fluorinated nucleophiles are particularly attractive because they provide access to pharmaceutically important fluorinated amino compounds.[4] Following Shibasaki's pioneering work on aldol-type reactions with nitriles,[5] silyl ketene imines that overcome some of the difficulties mentioned above have been used as reactive nitrile surrogates in asymmetric aldol and Mannich reactions.[6] The direct use of nitrile compounds, however, appears more appealing because it obviates the necessity to prepare a silyl ketene imine derivative. To this end, the introduction of Shibasaki's cooperative soft Lewis acid – hard Brønsted base catalysis strategy has significantly widened the substrate scope.[7] In recent years, several groups have achieved enantioselective catalytic Mannich additions to aldimines with nitriles carrying an adjacent carbonyl, sulfonyl or another activating functionality.[8] Decarboxylative methods and the catalytic addition of allenylnitriles, benzylnitriles or phenylthioacetonitrile to aldimines have also been reported by Shibasaki, Nakamura and others.[9]

Enantioselective Mannich reactions with ketimines have been accomplished with activated nitriles (Scheme 1a and b).[6j,10] To demonstrate the use of α-fluoro-α-substituted nitriles in asymmetric catalysis, we chose to investigate the possibility of a Mannich reaction with ketimines derived from isatin which affords an important scaffold encountered in many natural products and drugs.[11] Because this reaction establishes two chirality centers, we also recognized the importance of providing convenient access to all four stereoisomeric products, preferentially by easily adaptable diastereodivergent protocols.[12] We now wish to report a (bisphosphine)copper(I) catalyzed direct asymmetric addition of α-fluoro-α-arylnitriles to isatin ketimines that addresses these challenges (Scheme 1c). Our method provides efficient access to multifunctional α-fluoro β-aminonitriles bearing vicinal tetrasubstituted stereocenters in high yields and with excellent enantio- and diastereoselectivity. Moreover, all four stereoisomers are accessible by suitable selection of the chiral copper catalyst and the isatin protecting group. The practical diastereodivergence, amenability to upscaling and selective functional group manipulation of the fluorinated α,β-aminonitrile moiety toward multifunctional β-fluoro-α,γ-diamines, α-fluoro-β-amino amides and fluorinated α-amino acid derivatives underscore the synthetic utility of this reaction.

At the beginning of our search for a stereodivergent catalytic asymmetric Mannich reaction, we chose α-fluorobenzylnitrile, **1a**, and the isatin derived *N*-Boc ketimines **2a-c** as test compounds and screened various Cu(I) salts, Segphos and Biphep ligands (**L1**-**L4**), solvents and base additives (Table 1 and SI). We found that the desired α-fluoro-β-aminonitrile **3aa** can be obtained from the *N*-benzyl isatin derived ketimine **2a** in 91% yield using catalytic amounts of copper(I) triflate, DTBM-Segphos (**L1**) and diisopropylethylamine as base in toluene, albeit with low stereoselectivities (entry 1). The enantio- and diastereoselectivity increased significantly to 80% *ee* and 5.2:1 dr when the *N*-trityl ketimine **2b** was employed (entry 2). Extensive variation of bisphosphine and phosphinooxazoline ligands (**L1**-**L8**) and the introduction of amidine and guanidine bases further improved results (entries 3–13). We were pleased to observe almost quantitative formation of *anti*-**3ab** with 83% *ee* and 6.7:1 dr using 10 mol% of copper hexafluorophosphate, **L1** and BTMG in toluene at room temperature (entry 5). A decrease in the reaction temperature finally allowed us to optimize the stereoselectivities and we isolated *anti*-**3ab** in 95% yield, 90% *ee* and 12.3:1 dr at −35 °C (SI and entry 14). Additional investigation of the reaction outcome revealed that the diastereoselectivity can be switched with C_1-symmetric bisphosphine ligands **L9**-**L14**. Using 5 mol% of $CuPF_6$ and BTMG, the opposite diastereomer was favored when 1,2-ferrocenyl bisphosphines were used as ligands (Table 1, entries 15–19). Poor stereoselectivities were initially observed until we resorted to the *N*-benzyl or *N*-phenyl ketimines and copper catalysts carrying either the Taniaphos ligands **L9** and **L14** or Walphos ligands **L11**-**L13** under otherwise identical reaction conditions. We found that (Walphos)Cu(I) favors high diastereoselectivities while the use of Taniaphos as chiral ligand leads to superior *ee's*. For example, the Mannich reaction between **1a** and **2a** gave *syn*-**3aa** in 99% yield with 13.4:1 dr and 70% *ee* which further increased to 80% when **L13** was replaced with Taniaphos **L14** (entries 20–22). The introduction of the *N*-phenyl isatin derived ketimine **2c** resulted in excellent enantioselectivity and we obtained *syn*-**3ac** in 94% yield with 98% *ee* and 3.0:1 dr using 5 mol% of **L14**, $CuPF_6$ and BTMG at −35 °C (entry 23).

Having optimized the Mannich reaction conditions and with practical stereodivergent protocols in hand, we continued with the evaluation of the substrate scope using a variety of α-fluoro-α-arylacetonitriles (Scheme 2). The (DTBM-Segphos) Cu(I)/BTMG catalyzed reaction with the α-fluoro-arylacetonitriles **1a**-**1i** and ketimine **2b** gave quantitative yields and high stereoselectivities demonstrating excellent functional group tolerance of electron-withdrawing and electron-donating substituents in the *ortho*-, *meta*-, *para*-positions of the phenyl ring. It is noteworthy that the reaction with the chloro- and bromo-substituted α-fluorobenzylnitriles **1b** and **1c** furnished *anti*-**3bb** and *anti*-**3cb** in 97–98% yield, more than 35:1 dr and 97% *ee*. Addition of α-fluoro-3,5-dimethoxybenzylnitrile **1i** to ketimine **2b** produced 83% of *anti*-**3ib** with more than 50:1 diastereoselectivity and 91% *ee*. Excellent results were also obtained with fluoroacetonitriles **1j-l** carrying 1,3-benzodioxole-5-yl, 2-naphthyl, or 2-fluorenyl rings. The corresponding α-fluoro-β-aminonitriles *anti*-**3jb**-**lb** were produced in high yield and with up to 45:1 dr and 93% *ee*.

Slow evaporation of a solution of **3ab** in ethanol and of **3lb** in a hexane/diethyl ether/dichloromethane (2:2:1) solution led to the formation of single crystals.[13] Crystallographic

analysis revealed *R* configuration at the oxindole C3 position and *S* configuration at the fluorinated carbon atom, and NMR and chiral HPLC measurements proved that these single crystals relate to the major stereoisomer formed using ((*R*)-DTBM-Segphos)Cu(I) as catalyst. The reactivity substituted *N*-trityl isatin derived ketimines **2d**-**2h** was also probed (Scheme 3). The presence of methyl, ethyl, and methoxy groups in the 5- or 6-position of the isatin moiety was well tolerated and we obtained high yields and stereoselectivities. All α-fluoro-β-aminonitriles were produced in high yields and with up to 34:1 dr and 96% *ee*.

We then evaluated the substrate scope for the diastereodivergent protocol using 5 mol% of ((*S,Sp*)-Taniaphos)Cu(I) as catalyst (Scheme 4). The reaction of five different α-fluoroarylacetonitriles to the *N*-phenyl isatin ketimine **2c** gave *syn*-**3ac**-**3kc** in 84–99% yield and with good to high stereoselectivities ranging from 3:1 to 7:1 dr and 83–97% *ee*, respectively. We obtained a single crystal of **3ic** by slow evaporation of a hexanes/ethanol/chloroform (3:1:1) solution. The crystallographic analysis is in agreement with NMR and chromatographic measurements which confirmed the favored formation of the *syn*-(*S,S*)-diastereomer.

Based on NMR analysis and in analogy to previously reported mechanistic studies we propose the catalytic cycle and a plausible transition state shown in Scheme 5 (SI).[8d,g,9c] Competition binding experiments revealed preferential binding of the α-fluorobenzylnitrile **1a** to the (Segphos)Cu(I) complex in the presence of the ketimine **2**. We then conducted H/D exchange and titration experiments and observed that the metal coordination of the nitrile significantly accelerates the reversible deprotonation of complex **A** to the cuprous keteniminate complex **B**. Irreversible C-C bond formation affords **C** which undergoes proton transfer and dissociation to **3**, regenerating the free Cu(I) complex and BTMG. In the favored transition state, the *N*-cuprated ketenimine exposes the *Si*-face for nucleophilic attack by the isatin ketimine which is expected to occupy a tilted orientation to minimize steric repulsion as the large *N*-trityl group occupies the bottom left axial space and the *N*-carbamoyl resides in the top right axial space. This exposes the *Si*-face of the ketimine and gives the (*R,S*)-diastereomer as observed.

Finally, the possibility of upscaling and the synthetic utility of the synthesized α-fluoro-β-aminonitriles were investigated (Scheme 6). We were pleased to find that nearly one gram of *anti*-**3ab** was produced in quantitative amounts and without compromised stereoselectivities using 5 mol% of the (DTBM-Segphos)Cu(I) catalyst. Reduction of compound **3ab** with $NaBH_4$ in the presence of $NiCl_2$ produced β-fluoro-α,γ-diamine **4** in 65% yield.[14] Hydrolysis of the cyano group in **3ab** using a catalytic amount of $Pd(OAc)_2$ and PPh_3 with acetaldoxime in aqueous EtOH gave the α-fluoro-β-amino amide **5**, a fluorinated analogue of the cholecystokinin-2 (CCK2)/gastrin receptor antagonist AG-041R,[15] in 97% yield.[16] Methanolysis with sodium methoxide opened the oxindole lactam ring in **3ab** without erosion of the original *ee* and dr, producing β-fluoro-α-amino acid methyl ester **6**, a fluorinated unnatural amino acid derivative.[17] Simultaneous deprotection of the trityl and Boc groups in **3ab** gave 76% of **7** in 89% ee and 12:1 dr. Our protocol can also be applied to α-alkyl-α-arylnitriles. We obtained **9** from α-methylphenylacetonitrile, **8**, in 96% yield and with 85% ee and more than 19:1 dr.

In summary, we have developed an efficient diastereodivergent catalytic enantioselective Mannich reaction constructing α-fluoro-β-aminonitriles bearing vicinal tetrasubstituted stereocenters *via* (bisphosphine)copper(I) complex/guanidine catalyzed addition of α-fluoroarylacetonitriles to isatin derived *N*-Boc ketimines. The switching of diastereoselectivity is very practical and can be conveniently achieved by properly choosing the chiral bisphosphine ligand and the isatin *N*-protecting group. Using either Segphos or Taniaphos-derived copper(I) complexes and BTMG as base we have prepared a variety of *syn*- and *anti*-diastereomers of multifunctionalized 3-aminooxindoles with an adjacent quaternary C-F stereocenter in excellent yields and *ee*'s. The reaction can be conducted at the gram scale without compromising yield and stereoselectivity and the general utility of α-fluoro β-aminonitriles was demonstrated with selective transformations of the nitrile functionality and oxindole ring opening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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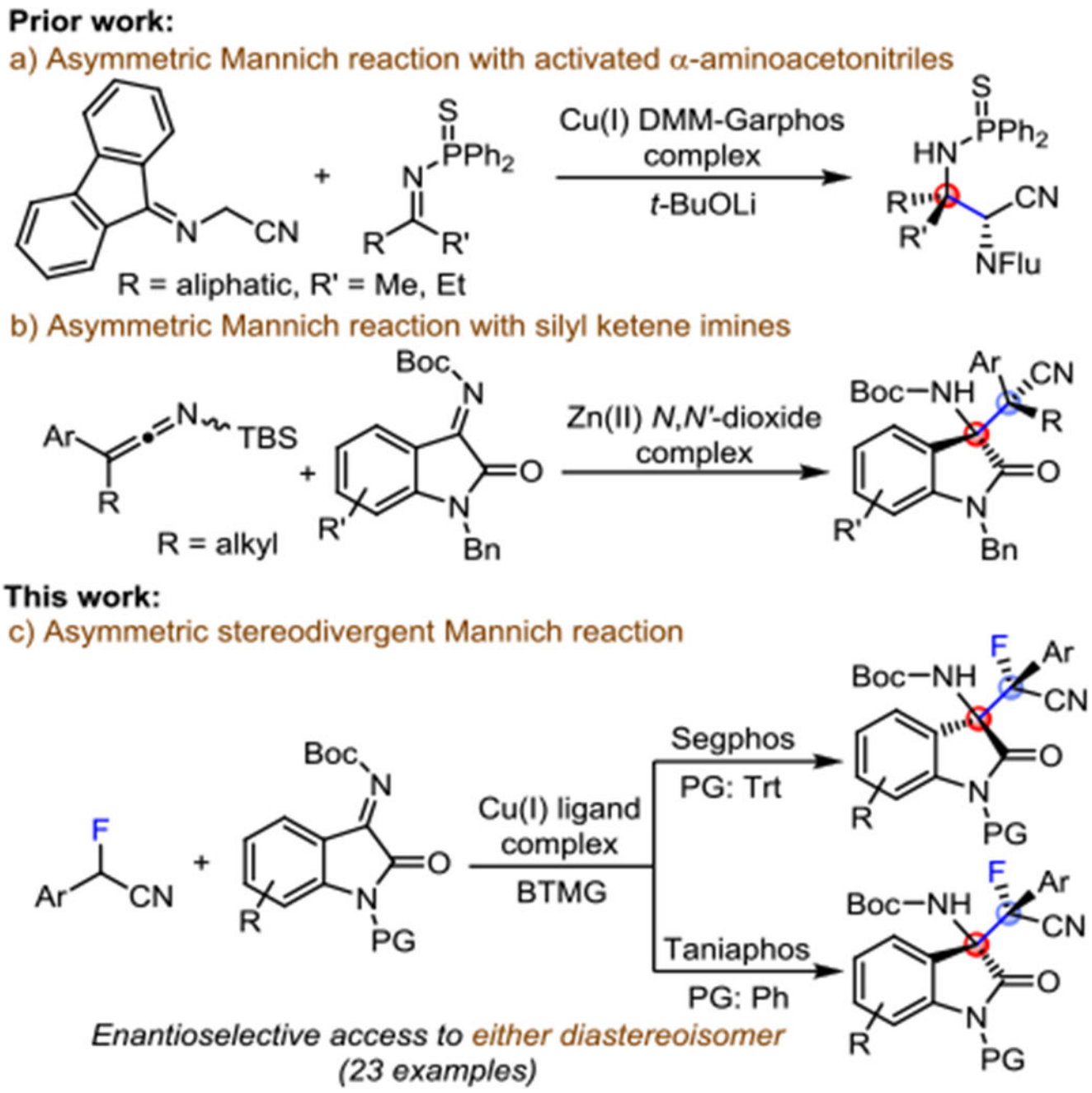
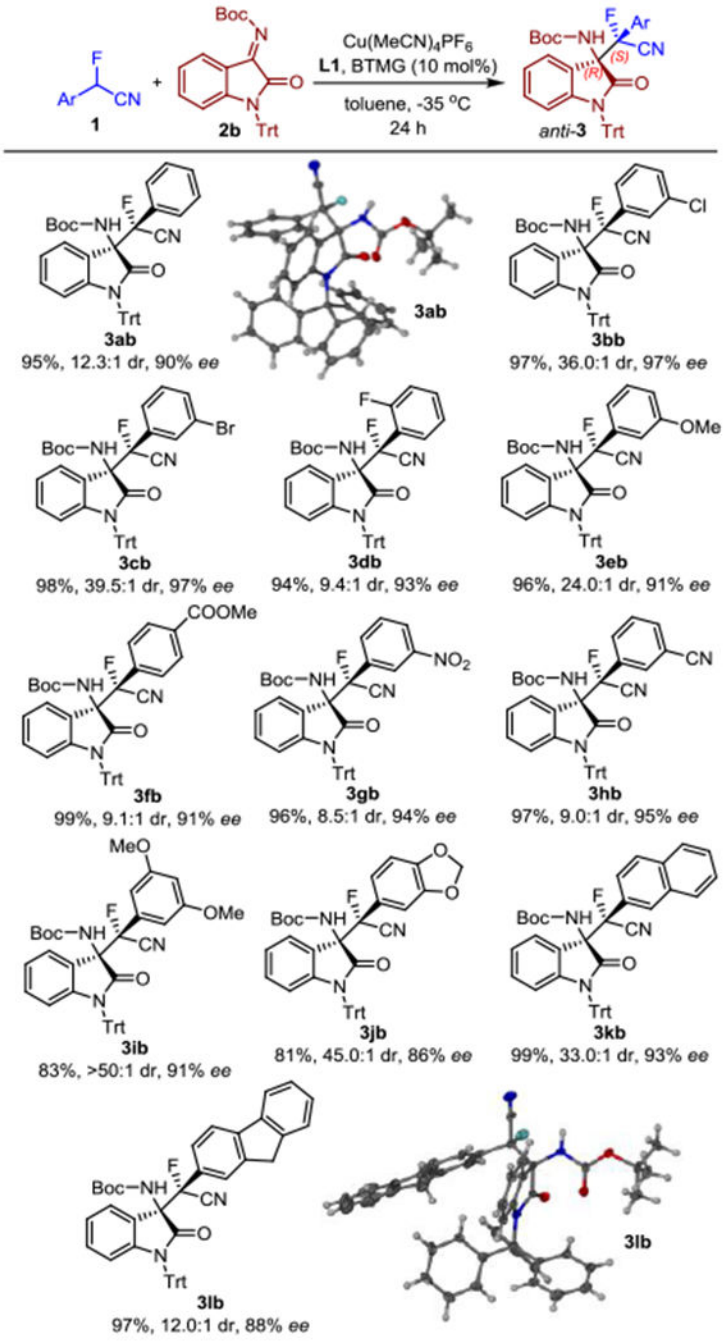
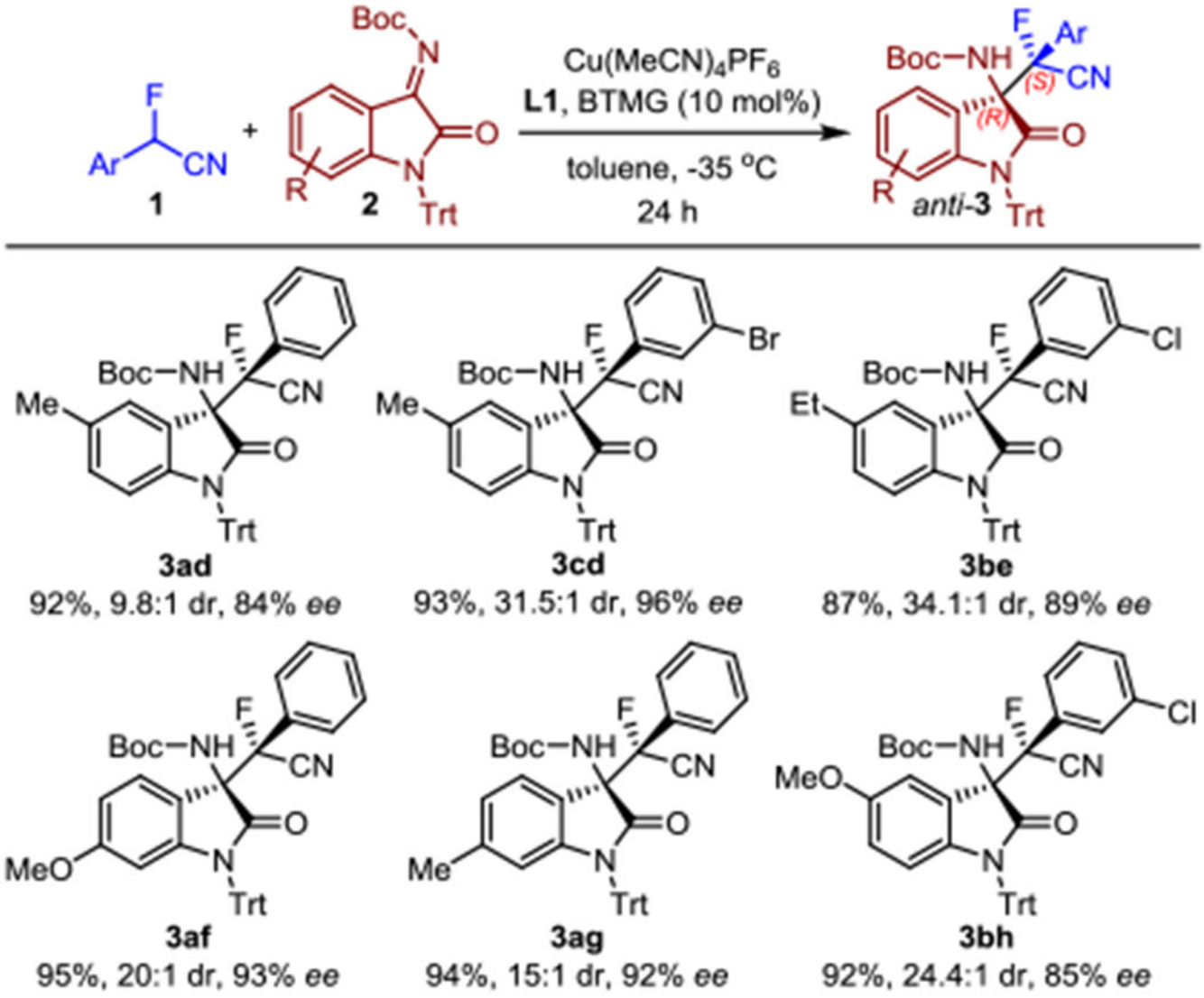


Scheme 1.
Synthesis of chiral β-aminonitriles bearing vicinal tetrasubstituted stereocenters.



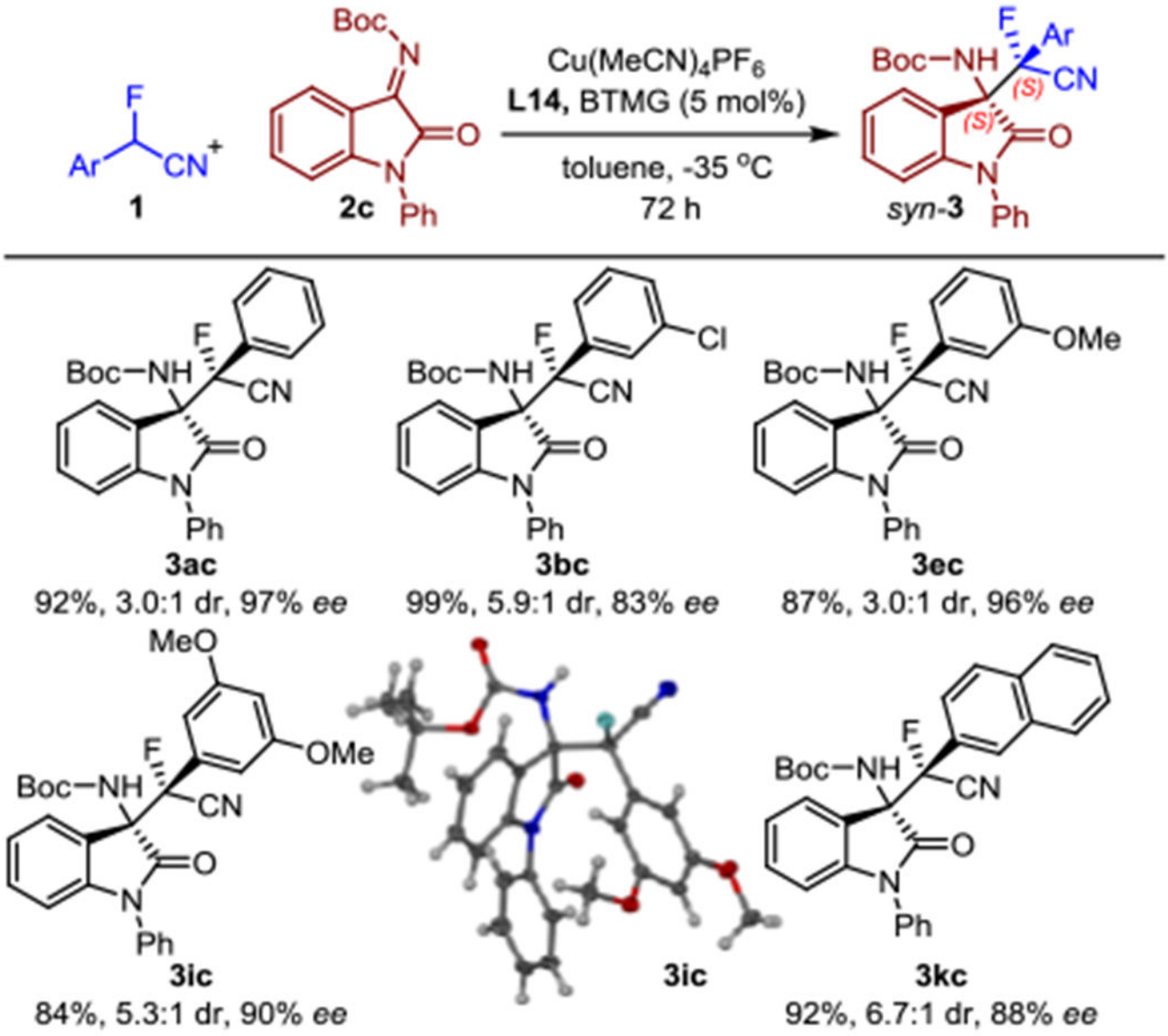
Scheme 2.

Reaction scope with α-fluoro-α-arylnitriles. The absolute configuration of 3ab and 3lb were determined by crystallographic analysis. The configuration of the other compounds was assigned by analogy.



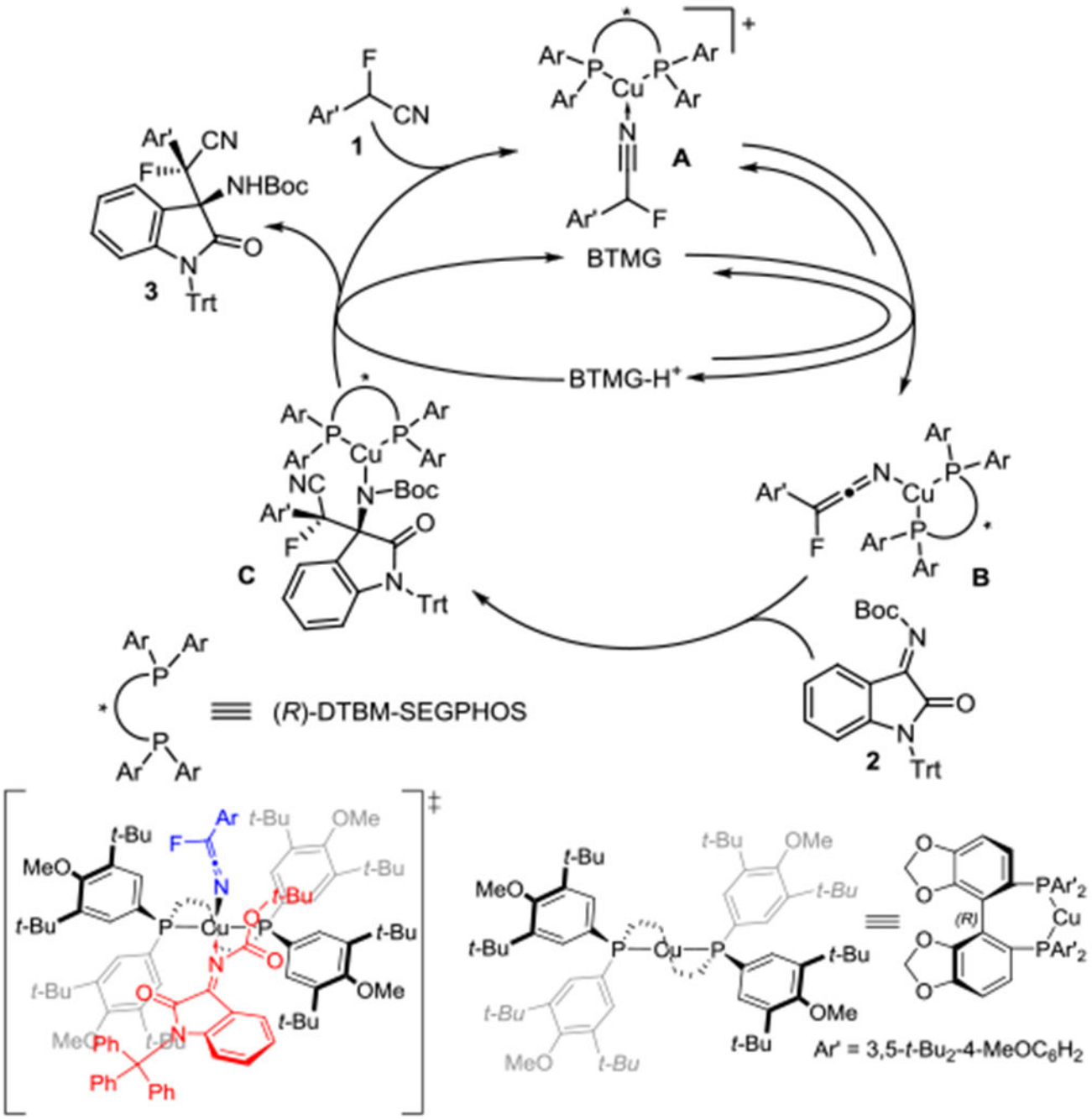
Scheme 3.

Reaction scope with *N*-trityl isatin derived *N*-Boc ketimines.

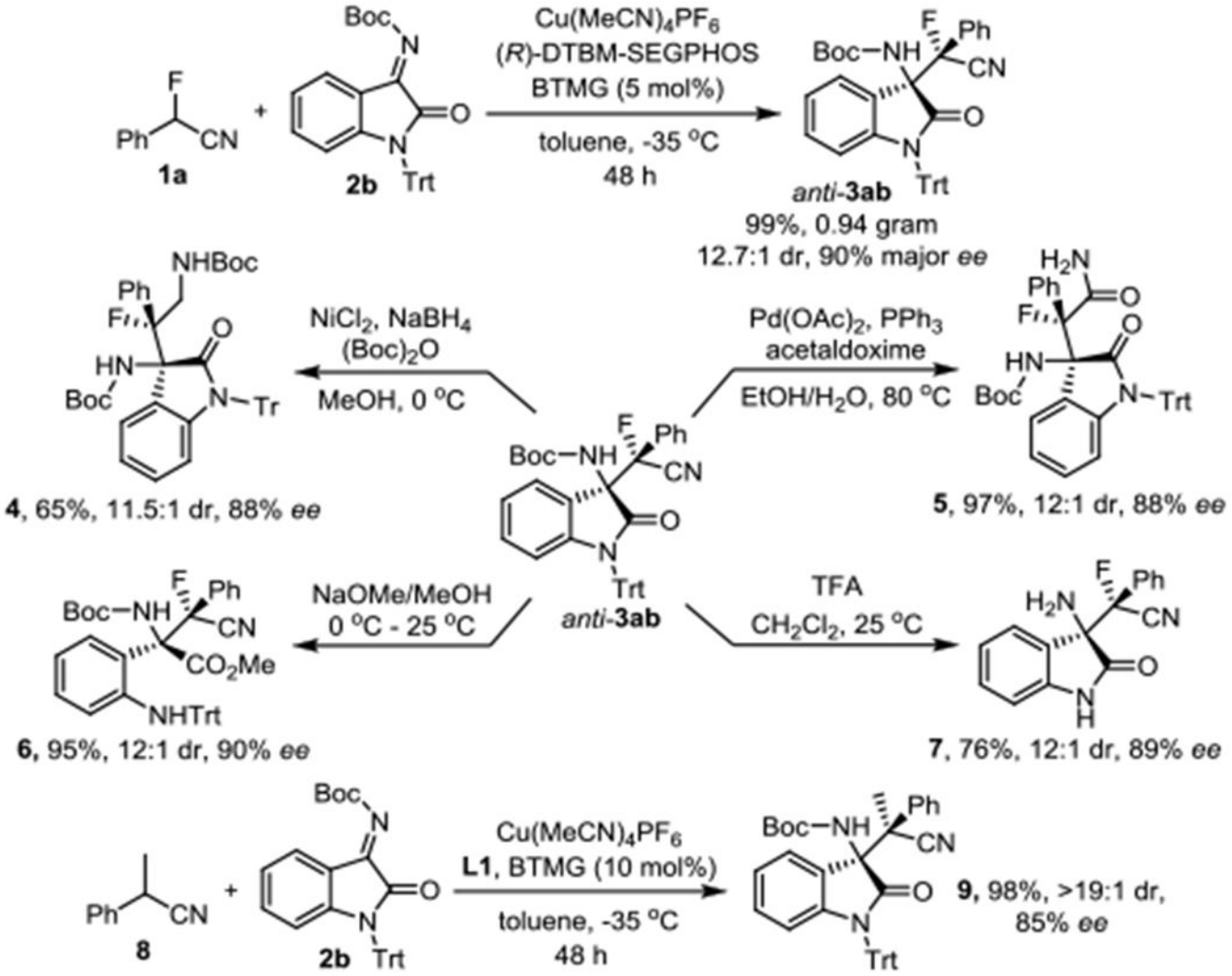


Scheme 4.

Diastereodivergent synthesis *syn*-α-fluoro-β-aminonitriles from *N*-phenyl isatin *N*-Boc ketimines using ((*S,Sp*)-Taniaphos)Cu(I) as catalyst.



Scheme 5.
Proposed mechanism.

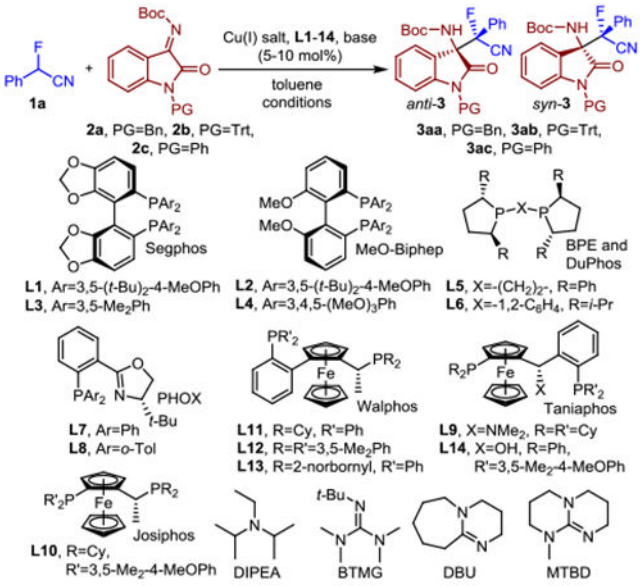


Scheme 6.

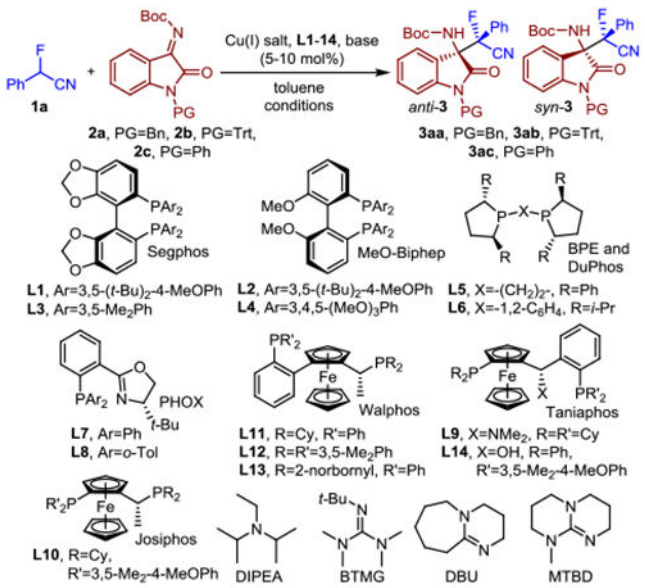
Gram scale synthesis, transformations of α-fluoro-β-aminonitrile 3ab and extension of the substrate scope to α-alkyl-α-arylnitriles.

Table 1.

Optimization of the stereodivergent asymmetric Mannich reaction.



Entry	Cu(I) source	Ligand	2	Conditions	Yield (%)	dr[a] (*anti*/*syn*)	*ee*[b] (%)
1	$Cu(PhMe)_{0.5}OTf$	**L1**	**2a**	DIPEA[c], 25 °C	91	1.7:1	41
2	$Cu(PhMe)_{0.5}OTf$	**L1**	**2b**	DIPEA[c], 25 °C	85	5.2:1	80
3	$Cu(PhMe)_{0.5}OTf$	**L2**	**2b**	DIPEA[c], 25 °C	74	4.6:1	75
4	$Cu(PhMe)_{0.5}OTf$	**L1**	**2b**	BTMG, 25 °C	98	5.8:1	83
5	$Cu(MeCN)_4PF_6$	**L1**	**2b**	BTMG, 25 °C	98	6.7:1	83
6	$Cu(MeCN)_4PF_6$	**L1**	**2b**	DBU, 25 °C	99	6.6:1	73
7	$Cu(MeCN)_4PF_6$	**L1**	**2b**	MTBD, 25 °C	99	5.8:1	83
8	$Cu(MeCN)_4PF_6$	**L3**	**2b**	BTMG, 25 °C	99	2.0:1	26
9	$Cu(MeCN)_4PF_6$	**L4**	**2b**	BTMG, 25 °C	99	4.0:1	79
10	$Cu(MeCN)_4PF_6$	**L5**	**2b**	BTMG, 25 °C	99	1.5:1	50
11	$Cu(MeCN)_4PF_6$	**L6**	**2b**	BTMG, 25 °C	99	1.5:1	31
12	$Cu(MeCN)_4PF_6$	**L7**	**2b**	BTMG, 25 °C	99	1.3:1	40
13	$Cu(MeCN)_4PF_6$	**L8**	**2b**	BTMG, 25 °C	99	1.1:1	47
14	$Cu(MeCN)_4PF_6$	**L1**	**2b**	BTMG, −35 °C	95	12.3:1	90
15[d]	$Cu(MeCN)_4PF_6$	**L9**	**2b**	BTMG, 25 °C	97	1:1.6	3
16[d]	$Cu(MeCN)_4PF_6$	**L9**	**2a**	BTMG, 25 °C	99	1:5.7	31
17[d]	$Cu(MeCN)_4PF_6$	**L10**	**2a**	BTMG, −35 °C	75	1:2.5	4
18[d]	$Cu(MeCN)_4PF_6$	**L11**	**2a**	BTMG, −35 °C	99	1:7.3	19



Entry	Cu(I) source	Ligand	2	Conditions	Yield (%)	dr[a] (*anti*/*syn*)	*ee*[b] (%)
19[d]	$Cu(MeCN)_4PF_6$	**L12**	**2a**	BTMG, −35 °C	99	1:5.6	60
20[d]	$Cu(MeCN)_4PF_6$	**L13**	**2a**	BTMG, −35 °C	99	1:13.4	70
21[d]	$Cu(MeCN)_4PF_6$	**L13**	**2c**	BTMG, −35 °C	98	1:8.7	75
22[d]	$Cu(MeCN)_4PF_6$	**L14**	**2a**	BTMG, −35 °C	94	1:5.7	80
23[d]	$Cu(MeCN)_4PF_6$	**L14**	**2c**	BTMG, −35 °C	94	1:3.0	98

Reaction condition: **1a** (0.055 mmol), **2** (0.050 mmol), Cu(I) source (0.005 mmol), ligand (0.006 mmol) and base in 0.3 mL toluene.

[a]Determined by ^{19}F NMR analysis.

[b]Determined by chiral HPLC analysis.

[c]The base loading was 80 mol%.

[d]The Cu complex and base loading were 5 mol%.