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Tris(oxazoline)/copper-catalyzed coupling of alkynes with nitrones: a highly enantioselective access to β-lactams

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ABSTRACT

Chiral tris(oxazoline)/Cu(I) complexes are demonstrated as a type of efficient catalysts for the asymmetric Kinugasa reaction of terminal alkynes with *C*-arylnitrones, providing a highly enantio- and diastereoselective access to optically active β-lactams.

1. Introduction

Chiral β-lactam is a key structure of many biologically active molecules,[1] such as penicillin, cephalosporin, thienamycin, and also a type of useful and extensively employed synthetic intermediates[2] in modern organic synthesis, enabling them as one of the best known four-membered heteocycles. Among the approaches for their asymmetric synthesis,[3,4] the enantioselective catalytic Kinugasa reaction[4] of alkynes with nitrones has attracted much attention and significantly advanced in the last decade, due to the readily available starting material and high functional group tolerance.

Inspired by the pioneering work of Kinugasa and Hashimoto,[5] Miura and co-workers reported the first asymmetric catalytic version of the Kinugasa reaction in 1995 and obtained up to 57% ee in the coupling of phenylacetylene and α,*N*-diphenylnitrone, using bis(oxazoline) (BOX) **1a**–**c**/CuI (Fig. 1) as the catalyst.[6] The first completely enantioselective Kinugasa reaction was reported in 2002 by Fu and co-workers, in which good to high enantioselectivities (up to 93% ee) and high cis-selectivities (up to >95:5 dr) were obtained with C_2-symmetric bis(azaferrocene) **2**/CuCl as the catalyst,[7a] and later they successfully extended this catalytic system to the intramolecular reaction by using planar-chiral ligand phosphaferrocene-oxazoline **3** instead.[7b] In 2003, our group demonstrated that a Cu(II) catalytic system in combination with tris(oxazoline) (TOX) **4** as a ligand is also effective for the Kinugasa reaction even under an air atmosphere and without rigorously dry conditions, and this 'sidearm' modification of BOX ligands provided up to 85% ee and up to 97:3 dr.[8] In this reaction, catalytically active Cu(I) species are supposed to be generated in situ upon the reduction of Cu(II) by phenylacetylene. Basak and co-workers discovered L-proline can also be used as a ligand in the Cu(I)-mediated Kinugasa reaction, and up to 15% ee was observed in the synthesis of exomethylene β-lactams.[9] Recently, Guiry and co-workers applied HETPHOX ligands **5a**–**c** in the Kinugasa reaction, and achieved a moderate level of enantioselectivity (up to 55% ee).[10] In a book chapter, Evans and co-workers disclosed a highly stereoselective copper-catalyzed coupling reaction of alkynes with nitrones using IndaBOX ligand **6a**, and up to 97:3 dr and up to 98% ee were obtained with a preference for the *C*-alkylnitrones.[11] IndaBOX ligands **6b** was also employed by Saito, Otani and co-workers in a recent report.[12] Therefore, only a quite limited number of highly enantioselective Kinugasa reactions have appeared so far, and there remains a substantial space for the improvement of both the yield and stereoselectivity. In fact, although high enantioselectivity has been achieved with certain type of substrates, to develop a highly efficient and enantioselective catalytic Kinugasa reaction is still a challenging task.

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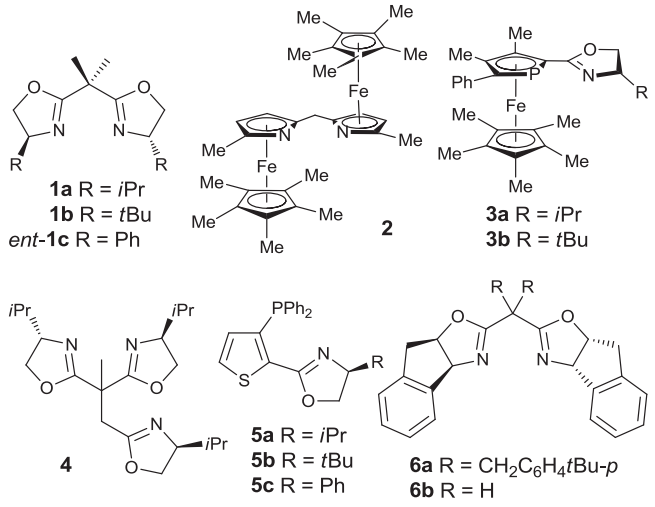


Fig. 1. Typical chiral ligands for asymmetric Kinugasa reactions.

2. Results and discussion

In our previous study, we have demonstrated that the introduction of an additional oxazoline 'sidearm' can not only accelerate the Kinugasa reaction but also improve the stereoselectivity.[8,13] In the following years, much effort has been devoted to this subject to further improve the performance of this system. We wish to report here a novel TOX/copper catalyst, with which a highly enantio- and diastereoselective coupling reaction of alkynes with *C*-arylnitrones was realized.

Pseudo C_3-symmetric IndaTOX **10a**, which was recently developed in our group and has shown excellent enantioselectivity in the Nazarov reaction,[13j] was chosen as a typical TOX ligand for the reaction optimization. The effect of the copper source was first examined under the standard reaction conditions established in our previous study, using acetonitrile as the solvent and dicyclohexylamine as the base.[8] As revealed in Table 1, $Cu(ClO_4)_2\cdot 6H_2O$ was efficient for the coupling reaction of phenylacetylene **7a** and nitrone **8a**, and *cis* β-lactam **9a** was obtained in 88% ee as the predominant diastereoisomer (entry 1). Other Cu(II) salts, such as $Cu(OAc)_2$, $CuSO_4$, and $CuBr_2$ were less active and selective (entries 2–4), while $Cu(BF_4)_2$ and $Cu(OTf)_2$ delivered the desired product with a similar level of stereoselectivity to $Cu(ClO_4)_2\cdot 6H_2O$ (entries 5–6 vs entry 1). To our delight, CuOTf·Tol was found as the most efficient copper salt, providing 90% ee and 90:10 dr (entry 9). The corresponding Cu(II) salt $Cu(OTf)_2$ was more active but the stereoselectivity was slightly lower (entry 6). It is noteworthy that in Saito's work CuOTf was found inactive in the IndaBOX-mediated reaction.[12] With respect to both the yield and stereoselectivity, salt CuOTf·Tol was employed as the copper source for the subsequent elaboration of the ligands.

To examine the influence of the sidearm group (R), a series of chiral oxazoline moieties was introduced into the IndaBOX scaffold (Fig. 2). As revealed in Table 2, *tert*-butyl substituted TOX **10c** proved to be the ligand of choice, giving a fast time (14 h) together with high cis- and enantioselectivity (90/10 cis/trans, 95% ee, entry 2). Compared with trisoxazoline/Cu(I) complex, the reaction with the parental bisoxazoline ligand **11** was much slower (44 h, entry 6) and less enantioselective. It is worth noting that the improvement of the enantioselectivity from 88% ee to 95% ee at 0 °C requires an additional energy difference of ca. 0.4 kcal/mol to be created between the two diastereomeric isomers of the transition state, which lead to the two opposite enantiomers (R and S) of the product.[14]

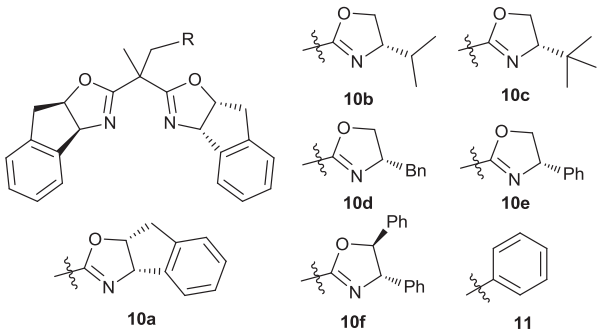
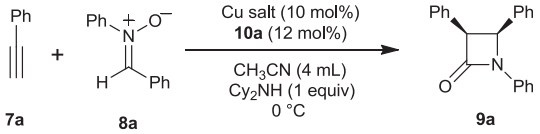


Fig. 2. Ligands designed based on a 'sidearm' strategy.

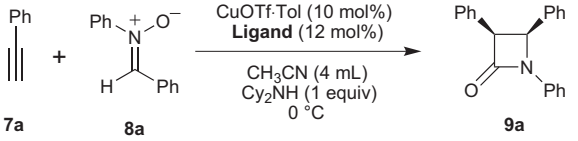
Table 1
The influence of the copper source[a]



Entry	Copper source	Time (h)	% Yield[b]	cis/trans[c]	% ee[d]
1	$Cu(ClO_4)_2\cdot 6H_2O$	18	65	90/10	88
2	$Cu(OAc)_2$	66	59	94/6	66
3	$CuSO_4$	66	51	90/10	65
4	$CuBr_2$	42	65	90/10	69
5	$Cu(BF_4)_2$	42	64	88/12	87
6	$Cu(OTf)_2$	27	63	87/13	88
7	CuI	26	69	92/8	63
8	CuBr	26	70	87/13	65
9	CuOTf·Tol	39	68	90/10	90

[a] TOX **10a** (0.5 mmol scale, 12 mol %), Cu salts (10 mol %), N_2.
[b] Total isolated yield of cis and trans-isomers.
[c] Determined by ^1H NMR.
[d] ee's of cis isomers, determined by chiral HPLC.

Table 2
Effect of the sidearm group[a]

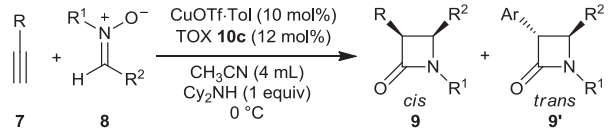


Entry	Ligand	Time (h)	% Yield[b]	cis/trans[c]	% ee[d]
1	**10b**	17	69	92/8	92
2	**10c**	14	67	90/10	95
3	**10d**	36	69	89/11	92
4	**10e**	14	68	84/16	91
5	**10f**	38	71	91/9	88
6	**11**	44	69	93/7	88

[a] Ligand (0.5 mmol scale, 12 mol %), CuOTf·Tol (10 mol %), N_2.
[b] Total isolated yield of cis and trans-isomers.
[c] Determined by ^1H NMR.
[d] ee's of cis isomers, determined by chiral HPLC.

Under the optimized reaction conditions, a range of alkynes and *C*-arylnitrones were examined, and the results are summarized in Table 3. Various β-lactams were obtained generally in good yields and high cis- and enantio-selectivities. The electronic nature of the *C*-aryl groups (R^2) showed little influence on the high enantioselectivity (entries 1–7). *N*-PMP protected nitrones are also appropriate substrates (entries 8–11) nitrone with a *para* ester substituent exhibited the highest reactivity, furnishing the desired β-lactam product in 98% yield in 6 h (entry 13). The current reaction also showed a good tolerance of different functionalities, such as halide, ether, ester, CF_3, and heterocycles (entry 13–18). Thus, the

Table 3
Substrate scope of the TOX/Cu-catalyzed Kinugasa reaction[a]



7 8 9 9'

Entry	R	R^1	R^2	% Yield[b,c] (cis/trans)	% ee[d]
1	C_6H_5	C_6H_5	C_6H_5	67(92/8)	95
2	C_6H_5	C_6H_5	*p*-MeC_6H_4	76(94/6)	92
3	C_6H_5	C_6H_5	*p*-$MeOC_6H_4$	71(95/5)	92
4	C_6H_5	C_6H_5	*p*-FC_6H_4	70(94/6)	96
5	C_6H_5	C_6H_5	*p*-ClC_6H_4	67(92/8)	93
6	C_6H_5	C_6H_5	*p*-$CF_3C_6H_4$	70(92/8)	93
7	C_6H_5	C_6H_5	*p*-$NO_2C_6H_4$	73(94/6)	92
8	C_6H_5	PMP	C_6H_5	73(95/5)	98
9	C_6H_5	PMP	*p*-$CF_3C_6H_4$	61(94/6)	94
10	C_6H_5	PMP	*p*-BrC_6H_4	67(94/6)	92
11	C_6H_5	PMP	PMP	61(95/5)	92
12	C_6H_5	*p*-MeC_6H_4	C_6H_5	61(91/9)	93
13	C_6H_5	*p*-$EtO_2CC_6H_4$	C_6H_5	98(89/11)	88
14	C_6H_5	*p*-BrC_6H_4	C_6H_5	74(93/7)	91
15	C_6H_5	C_6H_5	α-furyl	75(70/30)	93
16	*p*-BrC_6H_4	C_6H_5	C_6H_5	34(86/14)	92
17	PMP	C_6H_5	C_6H_5	72(95/5)	98.5
18	*p*-MeC_6H_4	PMP	*p*-$CF_3C_6H_4$	55(90/10)	93
19[e]	C_6H_5	C_6H_5	C_6H_5	80	>99
20	1-Cyclo-hexenyl	C_6H_5	C_6H_5	71(97/3)	96
21	*n*-Pentyl	C_6H_5	C_6H_5	74(97/3)	73

[a] TOX **10C** (0.5 mmol scale, 12 mol %), CuOTf·Tol (10 mol %), N_2.
[b] Total isolated yield of cis and trans-isomers.
[c] cis/trans ratios were determined by ^1H NMR.
[d] ee's of cis isomers, determined by chiral HPLC.
[e] Recrystallized from hexane/EtOAc/CH_2Cl_2, with *cis* **9a**.

introduction of an additional oxazoline moiety not only increased the performance of the parental IndaBOX ligand in the Kinugasa reaction of alkynes with *C*-arylnitrones, but also altered the substrate scope. To our knowledge, the diastereo- and enantioselectivities observed in this TOX/Cu-catalytic system are among the best results in the asymmetric catalytic Kinugasa reaction.[4] The current substrate scope of our system is also a good complement to the Evans' BOX/Cu system.[11] Moreover, the enantiomeric purity of cis product **9a** can be readily increased to >99% ee through a single recrystallization (entry 19). Alkynes also worked well to give the desired product with moderate to high ees (entries 21–22).

3. Conclusions

In summary, TOX **10c** was identified as an efficient ligand for the copper-catalyzed Kinugasa reaction of alkynes with *C*-arylnitrones. Both high diastereo- and enantioselectivity (up to 97:3 dr and 98.5% ee) have been achieved, providing an attractive approach for the synthesis of enantiomerically enriched β-lactams. Mechanistic study and further extension of the current reaction is underway.

4. Experimental section

4.1. General

Commercial solvents were dried and purified by standard procedures, as specified in 'Purification of Laboratory Chemicals'. Various alkyl amines were purchased from commercial suppliers and were distilled over potassium hydroxide pellets under N_2 atmosphere. Low- and high-resolution mass spectra were recorded by EI or ESI method. Optical rotations were determined at 589 nm (sodium D line) by using a Perkin–Elmer-341 MC digital polarimeter.

4.2. Typical procedure for the synthesis of chiral ligands

To a solution of Inda-bisoxazoline (0.65 g, 1.9 mmol) in dried THF (30 mL) was added dropwise *t*-BuLi (2 mL, 1.3 M in THF, 2.6 mmol) within 15–20 min at −78 °C. The resulting yellow solution was stirred for 1 h at the same temperature, then a solution of 2-chloromethyl oxazoline or benzyl bromide (2.8 mmol) in THF (10 mL) was added dropwise at −78 °C over 20 min. The mixture was slowly warmed to room temperature and kept stirring for a further 36 h. The solvent was removed and the residue was diluted with CH_2Cl_2 (100 mL), then washed with H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2×20 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/acetone=10/1) to afford the desired product. The syntheses and characterizations of ligands **10a–c** have been reported before.[13j,15]

*4.2.1. (3aS,3a′S,8aR,8a′R)-2,2′-(1-((S)-4-Benzyl-4,5-dihydrooxazol-2-yl)propane-2,2-diyl)bis(8,8a-dihydro-3aH-indeno [1,2-d] oxazole) (**10d**).* White solid, 56% yield; $[\alpha]_D^{20}$ −200.0 (*c* 0.715, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.50–7.46 (m, 2H), 7.28–7.16 (m, 9H), 7.06 (d, *J*=6.9 Hz, 2H), 5.57 (d, *J*=2.7 Hz, 1H), 5.54 (d, *J*=2.7 Hz, 1H), 5.32–5.27 (m, 2H), 4.06–4.02 (m, 1H), 3.47–3.25 (m, 4H), 3.02 (dd, *J*=18.0 Hz, 7.8 Hz, 2H), 2.98 (s, 2H), 2.78 (dd, *J*=13.8, 5.1 Hz, 1H), 2.32 (dd, *J*=13.8, 8.7 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.5, 167.0, 163.8, 141.6, 141.5, 140.1, 139.5, 137.8, 129.1, 129.0, 128.6, 128.4, 128.2, 128.1, 127.2, 127.0, 126.2, 125.6, 125.5, 125.4, 125.0, 124.8, 83.4, 83.3, 76.4, 76.3, 76.2, 70.8, 66.8, 41.1, 40.6, 39.5, 39.4, 34.5, 20.8; IR (neat): 3025, 2923, 2853, 1649, 1458, 1227, 1162, 1095, 1019, 986, 857, 750, 702 cm^{-1}; LRMS-ESI (*m*/*z*): 518.2 ($M+H^+$); HRMS-ESI (*m*/*z*): calcd for $C_{33}H_{32}N_3O_3^+$, 518.2453; found, 518.2438.

*4.2.2. (3aS,3a′S,8aR,8a′R)-2,2′-(1-((S)-4-Phenyl-4,5-dihydrooxaz-ol-2-yl)propane-2,2-diyl)bis(8,8a-dihydro-3aH-indeno[1,2-d]oxazole) (**10e**).* White solid, 71% yield; $[\alpha]_D^{20}$ −226.5 (*c* 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.52–7.47 (m, 2H), 7.30–7.18 (m, 9H), 7.09 (d, *J*=6.9 Hz, 2H), 5.58 (d, *J*=7.8 Hz, 1H), 5.55 (d, *J*=7.8 Hz, 1H), 5.34–5.27 (m, 2H), 4.86 (t, *J*=9.2 Hz, 1H), 3.64–3.55 (m, 2H), 3.67–3.26 (m, 2H), 3.07–2.97 (m, 4H), 1.55 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.4, 167.0, 164.7, 142.1, 141.7, 141.5, 140.1, 139.5, 128.4, 128.3, 128.2, 127.3, 127.2, 127.0, 126.4, 125.5, 125.0, 124.9, 83.4, 76.4, 76.3, 73.8, 69.2, 40.7, 39.6, 39.4, 34.6, 20.9; IR (neat): 3025, 2922, 2852, 1649, 1479, 1427, 1347, 1277, 1227, 1161, 1097, 988, 856, 750, 700 cm^{-1}; LRMS-ESI (*m*/*z*): 504.2 ($M+H^+$); HRMS-ESI (*m*/*z*): calcd for $C_{32}H_{30}N_3O_3^+$, 504.2275; found, 504.2282.

*4.2.3. (3aS,3a′S,8aR,8a′R)-2,2′-(1-((4S,5S)-4,5-Diphenyl-4,5-dihydrooxazol-2-yl)propane-2,2-diyl)bis(8,8a-dihydro-3aH-indeno [1,2-d]oxazole) (**10f**).* White solid, 88% yield; $[\alpha]_D^{20}$ −82.5 (*c* 0.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.53–7.49 (m, 2H), 7.29–7.18 (m, 6H), 6.97–6.96 (m, 6H), 6.75–6.69 (m, 4H), 5.59 (d, *J*=7.8 Hz, 1H), 5.54 (d, *J*=7.5 Hz, 1H), 5.35–5.27 (m, 3H), 4.74 (d, *J*=9.9 Hz, 1H), 3.33–2.92 (m, 6H), 1.70 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 167.5, 167.1, 164.9, 141.8, 141.5, 140.2, 139.6, 137.4, 136.2, 128.2, 127.5, 127.4, 127.3, 127.0, 126.9, 126.6, 126.0, 125.5, 125.1, 125.0, 85.0, 83.4, 76.4, 73.1, 40.8, 39.6, 39.3, 35.2, 21.3; IR (neat): 3035, 2971, 2917, 1650, 1453, 1347, 1180, 1095, 993, 855, 753, 695 cm^{-1}; LRMS-ESI (*m*/*z*): 580.2 ($M+H^+$); HRMS-ESI (*m*/*z*): calcd for $C_{38}H_{34}N_3O_3^+$, 580.2585; found, 580.2595.

*4.2.4. (3aS,3a′S,8aR,8a′R)-2,2′-(1-Phenylpropane-2,2-diyl)bis(8,8a-dihydro-3aH-indeno[1,2-d]oxazole) (**11**).* White solid, 87% yield; $[\alpha]_D^{20}$ −279.7 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.50 (m, 1H), 7.38 (d, *J*=7.2 Hz, 1H), 7.34–7.23 (m, 6H), 7.01–6.97 (m, 1H),

6.84 (t, J=6.4 Hz, 2H), 6.74–6.73 (m, 2H), 5.55 (d, J=3.6 Hz, 1H), 5.53 (d, J=2.4 Hz, 1H), 5.33–5.26 (m, 2H), 3.34 (dd, J=18 Hz, 7.2 Hz, 2H), 3.23–3.11 (m, 3H), 3.03–2.98 (m, 1H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 167.9, 141.6, 141.6, 139.6, 139.5, 135.8, 129.9, 128.2, 128.2, 127.5, 127.3, 127.2, 126.2, 125.6, 125.5, 125.0, 124.9, 83.4, 82.9, 76.4, 76.2, 42.8, 41.4, 39.5, 39.2, 20.4; IR (neat): 3051, 2988, 2957, 2938, 2921, 1649, 1493, 1481, 1451, 1431, 1369, 1352, 1285, 1248, 1225, 1179, 1165, 1087, 1063, 1028, 1015, 991, 949, 939, 857, 838, 761, 741, 711, 701, 615, 598, 552 cm^{-1}; LRMS-ESI (m/z): 435.2 ($M+H^+$); HRMS-ESI calcd for $C_{29}H_{27}N_2O_2^+$: 435.2067, found, 435.2062.

4.3. General procedures for the coupling reaction of alkynes with nitrones

A mixture of CuOTf·Tol (26 mg, 0.05 mmol) and (*S*)-Inda trisoxazoline **10c** (29 mg, 0.06 mmol) in CH_3CN (4 mL) was stirred under N_2 at room temperature for 2 h. The solution was cooled to 0 °C, and then Cy_2NH (100 μL, 0.5 mmol) was added. After 10 min, alkyne (0.75 mmol) was added, followed by the addition of nitrone (0.5 mmol) after half an hour. After the reaction was completed (monitored by TLC), the mixture was passed through a short silica gel column (CH_2Cl_2 as the eluent). The filtrate was concentrated, and the residue was purified by flash chromatography (PE/CH_2Cl_2) to afford the product. The diastereoselectivity was determined by ^{1}H NMR spectroscopic analysis of the crude product. The determination of enantioselective excess of the cis-isomer was performed by chiral HPLC analysis with a Daicel Chiralcel AD-H/OD-H column (254 nm, eluent: hexane/^{i}PrOH=80/20, flow rate: 0.7 mL/min).

*4.3.1. (3S,4S)-4-(4-Fluorophenyl)-1,3-diphenylazetidin-2-one (**9d**).* Table 3, entry 4, 70% yield (solid, 25 h); $[\alpha]_D^{20}$ +2.1 (*c* 0.85, $CHCl_3$); ee is determined by HPLC analysis (Chiralcel OD-H, ^{i}PrOH/hexane=20/80, 0.7 mL/min, 254 nm; t_R (minor)=21.74 min, t_R (major)=8.85 min), 96% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J=1.2 Hz, 2H), 7.38–7.26 (m, 2H), 7.12–7.01 (m, 8H), 6.81–6.77 (m, 2H), 5.44 (d, J=6.0 Hz, 1H), 4.99 (d, J=6.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.4, 163.4, 161.0, 137.5, 131.9, 130.2, 130.2, 129.1, 129.0, 128.8, 128.7, 128.2, 127.3, 124.2, 117.1, 115.4, 115.2, 60.3, 59.6; IR (neat): 1744, 1597, 1496, 1456, 1416, 1377, 1265, 1225, 1157, 829, 733, 692 cm^{-1}; LRMS-EI (m/z): 317 (M^+); HRMS-EI calcd for $C_{21}H_{16}NOF^+$: 317.1216; found: 317.1219.

*4.3.2. (3S,4S)-1-(4-Methoxyphenyl)-3-(p-tolyl)-4-(4(trifluoromethyl)phenyl)azetidin-2-one (**9r**).* Table 3, entry 18, 55% yield (solid, 60 h); $[\alpha]_D^{20}$ −6.0 (*c* 2.25, $CHCl_3$); ee is determined by HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane=20/80, 0.7 mL/min, 254 nm; t_R (minor)=27.34 min, t_R (major)=13.64 min), 93% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J=8.0 Hz, 2H), 7.32–7.30 (m, 2H), 7.17 (d, J=8.0 Hz, 2H), 6.90–6.82 (m, 6H), 5.44 (d, J=6.0 Hz, 1H), 5.00 (d, J=6.0 Hz, 1H), 3.77 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.9, 156.2, 139.0, 137.2, 130.9, 129.0, 128.6, 128.4, 127.5, 125.2, 125.1, 118.3, 114.4, 60.2, 59.8, 55.4, 21.0; IR (neat): 2963, 1411, 1259, 1081, 1013, 866, 793, 701 cm^{-1}; LRMS-EI (m/z): 411 (M^+); HRMS-EI calcd. For $C_{24}H_{20}NO_2F_3^+$: 411.1446; found: 411.1449.

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Supplementary data

^{1}H NMR ^{13}C NMR for new compounds, and HPLC spectra for **9a**–**t**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.04.049.

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