Published in final edited form as:

ACS Catal. 2015 January 4; 6(1): 151–154. doi:10.1021/acscatal.5b02182.

Enantioselective Synthesis of Fluoro–Dihydroquinazolones and –Benzooxazinones by Fluorination-Initiated Asymmetric Cyclization Reactions

Kenichi Hiramatsu^{†,‡}, Takashi Honjo[†], Vivek Rauniyar[†], and F. Dean Toste^{*,†}

[†]Department of Chemistry, University of California Berkeley, California 94720, United States

[‡]Department of Medicinal Chemistry, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Chiyoda-ku, Tokyo 101-0062, Japan

Abstract

Stereoselective synthesis of two fluorine-bearing drug-like scaffolds, dihydroquinazolone and benzooxazinone, has been accomplished through asymmetric fluorocyclization reactions initiated by the fluorination process. The reaction employs double axially chiral anionic phase-transfer catalysts to achieve high diastereo- and enantioselectivities, and a wide range of fluorine-containing dihydroquinazolones were obtained (>20:1 dr, up to 98% ee).

Keywords

asymmetric synthesis; chiral anion; cyclization; fluorination; phase-transfer catalyst

The correlation between a molecule's carbon bond saturation ratio (Fsp³) and the existence of chiral centers with the success of drug candidates as they proceed from discovery to clinical development¹ makes the asymmetric construction of saturated, conformationally constrained rings an important objective in modern medicinal chemistry. Furthermore, the incorporation of fluorine into potential drugs has been identified as one of the most effective ways to optimize pharmacological properties,² for example, improving metabolic stability,³ lowering pK_a values of proximal amino groups,⁴ or tuning molecular conformations.⁵ Asymmetric fluorocyclization is an attractive strategy because it can provide direct access to

*Corresponding Author fdtoste@berkeley.edu.

Supporting Information The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b02182.

Experimental details and compound characterization data (PDF)

X-ray data for **2s** (CIF)

X-ray data for **2f** (CIF)

The authors declare no competing financial interest.

saturated rings bearing fluorine from readily accessible olefin substrates. Although a variety of fluorocyclization protocols have been developed,⁶ further catalytic asymmetric variants await development.⁷

In recent years, protocols for the asymmetric synthesis of two such pharmaceutically privileged scaffolds, dihydroquinazolinone and benzoxazinone,⁸ have been reported. These involve the chiral phosphoric acid-catalyzed reactions between anthranilamide or salicylamide and a range of aldehydes, as shown in eq 2.⁹ Given that the dihydroquinazolinone and benzoxazinone (*N,N*- and *N,O*-aminal moieties) are metabolically labile,¹⁰ it is of interest to explore the properties of their fluorinated analogues.¹¹ However, these compounds cannot be accessed using the current methodology due to the relative instability of the required α -fluoroaldehyde starting materials.^{12,13} Recently, our group implemented chiral anion phase-transfer catalysis achieving excellent enantioselectivity in a variety of fluorination reactions by employing lipophilic phosphate anions as catalysts that can undergo solubilizing anion metathesis with otherwise insoluble halogen sources such as Selectfluor (eq 1).¹⁴ As an alternative, we envisioned that *replacement of the protonation by fluorination* might enable access to the fluorinated variants of these important heterocycles. The phase transfer fluorination of enamide would generate an iminium-intermediate that would be intercepted by a tethered nucleophile to provide the drug-like scaffolds (eq 3).

Initially, dimethylenamides (eq 3, $R^2 = \text{Me}$) bearing suitable nucleophiles at the *ortho* positions were chosen as substrates in the hope that the nucleophiles would attack a transiently generated α -fluoroiminium ion and ion-paired intermediate to furnish the desired fluorocyclized product. The potential chiral phosphoric acid catalysts (*R*)-PhDAP, (*R*)-C₈-TRIP, and (*S*)-VAPOL phosphoric acid (PA)¹⁵ were investigated in view of their success in our previous asymmetric enamide fluorinations,^{14b,c} and the reported asymmetric amination of imines.¹⁵

(1)

Previous Work - Synthesis of Dihydroquinazolone and Benzoxazinone (List, Rueping)

(2)

This Work - Asymmetric Fluorocyclization with amine and oxygen nucleophiles

(3)

Molecular sieves (MS) were added to prevent potentially competitive fluorohydration reactions (Table 1).^{14c}

Reaction of a substrate bearing a free amino nucleophile (**1e**) with (*S*)-VAPOL PA or (*R*)-C₈-TRIP produced intermolecular fluoroaminated product **2e** in low yield and stereoselectivity, but use of (*R*)-PhDAP increased the enantioselectivity to 87% *ee* albeit with low (13%) yield (entry 3). In attempts to favor

the desired intramolecular reactivity, the *N*-methylated substrate **1f** was subjected to the reaction conditions, affording the desired fluorocyclization product at ambient temperature. The best result (72% yield, 84% *ee*, entry 6) was obtained using (*R*)-PhDAP. Under the optimized reactions conditions, substrate **1l** with a phenolic nucleophile furnished the desired oxyfluorinated product in high yield but with disappointing enantioselectivity, 55% *ee* and 36% *ee* using (*R*)-PhDAP and (*R*)-C₈-TRIP, respectively (entries 8 and 9), given our previous results on oxyfluorination using the same catalysts.^{14c} A catalyst screen revealed that both the previously reported (*R*)-OCyDAP¹⁶ and (*S*)-VAPOL PA afforded high yields and excellent enantioselectivities, 71% yield and 98% *ee*, 76% yield and 96% *ee*, respectively (entries 12 and 14).¹⁷

Next, the scope of amine nucleophiles was examined (Table 2).¹⁸ Reaction with carbamate substrate **1a** resulted in fluorohydrated product despite the addition of molecular sieves (entry 1). The analogous sulfonamide substrates afforded the products of fluorocyclization but gave low enantioselectivities (entries 2–4), reflecting the low nucleophilicity of the amide moieties. However, a wide range of *N*-monoalkylated substrates gave the desired fluorocyclized products in moderate yields (34–72% yield) and with high

enantioselectivities (84–94% ee), (entries 5, 6 in Table 2 and entry 6 in Table 1).¹⁹ With the *N*-phenyl substrate (**1i**), the reaction proceeded with excellent (90%) yield and stereoselectivity (98% ee, entry 7).²⁰ Both electron-donating and -withdrawing substituents on the phenyl ring were well tolerated (entries 8 and 9). The absolute stereochemistry of the products was unambiguously established as *R* by X-ray crystallographic analysis of compound **2f** (Supporting Information).

Having established the broad nucleophile scope, we next directed our attention to substitution of the anthranilamide scaffold (Table 3). A variety of electron-donating, neutral, and electron-withdrawing substituents at C4, C5, and C6 of this scaffold were well-tolerated (55–93% yield, 89–97% ee, entries 1–6).

We next investigated whether unsymmetrically substituted enamides could be employed in a previously challenging^{12b–d,14c} enantio- and diastereoselective fluoroamination reaction (Table 4²¹). Fluoroamination using the readily accessible (*E*)-phenylmethyl enamide (**1s**) under homogeneous conditions²² afforded the desired product as a 5:2 mixture of diastereomers. In contrast, the phase-transfer approach, using (*R*)-PhDAP as the catalyst, produced the desired product with excellent diastereoselectivity and moderate enantioselectivity (>20:1 dr, 57% ee, entry 1). By modifying the reaction conditions, using 4 Å molecular sieves in xylene, higher enantioselectivity (72% ee) was observed using (*R*)-PhDAP (entry 2). In attempts to further improve the selectivity, we prepared (*R*)-4-Ph-PhDAP, which features a biphenyl moiety at the 4 and 4' positions of the privileged *bis*-BINOL backbone, presumably generating a more confined chiral pocket by further extending the chiral information. Using this novel catalyst, product **2s** was obtained with high diastereo- and enantioselectivity (>20:1 dr, 87% ee, 42% yield, entry 2). Substitution of the phenyl ring at the *para* position was well-tolerated with both (*R*)-PhDAP and (*R*)-4-Ph-PhDAP providing high selectivities (>20:1 dr, 70–86% ee, 40–55% yield, entries 3 and 4). Finally, replacement of the phenyl with a thiophene ring showed promisingly high enantioselectivity (>20:1 dr, 72% ee, entry 5).²³

Substrates **1t** and **1v** decomposed when exposed to a homogeneous solution of Selectfluor in acetonitrile;²² however, the phase-transfer conditions afforded the desired products **2t** and **2v**, highlighting the ability of this strategy to suppress undesired background reactivity. Fluoroamination under homogeneous conditions²² or the use of other catalysts such as (*R*)-C₈TRIP showed diminished diastereoselectivity, reflecting that the stereocontrol by (*R*)-PhDAP and (*R*)-4-Ph-PhDAP is crucial to achieving high diastereoselectivity.²⁴

In summary, two kinds of pharmaceutically privileged fluorine-bearing scaffolds have been synthesized using chiral anionic phase-transfer catalysts. Importantly, high selectivities are not dependent on the fluorination generating a fluorine stereocenter and therefore imply that fluorination may be replaced by protonation in the processes, which were previously established under phosphoric acid catalysis. Further studies to disclose this hypothesis are ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We gratefully acknowledge NIHGM (R01 GM104534) for financial support. K.H. gratefully acknowledges support from Asubio Pharma. T.H. thanks Mitsubishi Tanabe Pharma Corporation, and V.R. thanks NSERC (Canada) for a postdoctoral fellowship.

REFERENCES

- (1). Lovering F, Bikker J, Humblet C. J. Med. Chem. 2009; 52:6752–6756. [PubMed: 19827778] For the conformational restriction in medicinal chemistry, see: Mann A. Wermuth CG. The Practice of Medicinal Chemistry (3rd. ed.). 2008:363–379. Academic Press London
- (2). For fluorine in medicinal chemistry, see: Böhm H-J, Banner D, Bendels A, Kansy M, Kuhn B, Müller K, Obst-Sander U, Stahl M. ChemBioChem. 2004; 5:637–643. [PubMed: 15122635] Shah P, Westwell AD. J. Enzyme Inhib. Med. Chem. 2007; 22:527–540. [PubMed: 18035820] Purser S, Moore PR, Swallow S, Gouverneur V. Chem. Soc. Rev. 2008; 37:320–330. [PubMed: 18197348] Hagmann WK. J. Med. Chem. 2008; 51:4359–4369. [PubMed: 18570365] O'Hagan D. Chem. Soc. Rev. 2008; 37:308–319. [PubMed: 18197347] Meanwell NA. J. Med. Chem. 2011; 54:2529–2591. [PubMed: 21413808]
- (3). Park BK, Kitteringham NR, O'Neill PM. Annu. Rev. Pharmacol. Toxicol. 2001; 41:443–470. [PubMed: 11264465]
- (4). Morgenthaler M, Schweizer E, Hoffmann-Röder A, Benini F, Martin RE, Jaeschke G, Wagner B, Fischer H, Bendels S, Zimmerli D, Schneider J, Diederich F, Kansy M, Müller K. ChemMedChem. 2007; 2:1100–1115. [PubMed: 17530727]
- (5). Hunter L. Beilstein J. Org. Chem. 2010; 6(38):1–14. [PubMed: 20485585]
- (6). (a) Sawaguchi M, Hara S, Fukuhara T, Yoneda N. J. Fluorine Chem. 2000; 104:277–280. (b) Serguchev YA, Lourie LF, Polishchuk GV, Chernega AN. Mendelev Commun. 2002; 12:115–117. (c) Zhou C, Ma Z, Gu Z, Fu C, Ma S. J. Org. Chem. 2008; 73:772–774. [PubMed: 18154357] (d) Wilkinson SC, Lozano O, Schuler M, Pacheco MC, Salmon R, Gouverneur V. Angew. Chem., Int. Ed. 2009; 48:7083–7086. (e) Shibata N, Tarui T, Doi Y, Kirk KL. Angew. Chem., Int. Ed. 2001; 40:4461–4463. (f) Wu T, Yin G, Liu G. J. Am. Chem. Soc. 2009; 131:16354–16355. [PubMed: 19856929] (g) Qian J, Liu Y, Zhu J, Jiang B, Xu Z. Org. Lett. 2011; 13:4220–4223. [PubMed: 21774521] (h) Li Z, Song L, Li C. J. Am. Chem. Soc. 2013; 135:4640–4643. [PubMed: 23506151] (i) Yang X, Wu T, Phipps RJ, Toste FD. Chem. Rev. 2015; 115:826–870. For a review, see: [PubMed: 25337896]
- (7). (a) Wang HF, Cui HF, Chai Z, Li P, Zheng CW, Yang YQ, Zhao G. Chem. - Eur. J. 2009; 15:13299–13303. [PubMed: 19899096] (b) Lozano O, Blessley G, Martinez del Campo T, Thompson AL, Giuffredi GT, Bettati M, Walker M, Borman R, Gouverneur V. Angew. Chem., Int. Ed. 2011; 50:8105–8109. (c) Kong W, Feige P, de Haro T, Nevado C. Angew. Chem., Int. Ed. 2013; 52:2469–2473. (d) Wolstenhulme JR, Gouverneur V. Acc. Chem. Res. 2014; 47:3560–3570. For a review, see: [PubMed: 25379791]
- (8). For examples of dihydroquinazolinone, see: Shetty BV, Campanella LA, Thomas TL, Fedorchuk M, Davidson TA, Michelson L, Volz H, Zimmerman SE, Belair EJ, Truant AP. J. Med. Chem. 1970; 13:886–895. [PubMed: 5458377] Synthesis of antihypertensive drug Metolazone: Cohen E, Klarberg B, Vaughan JR Jr. J. Am. Chem. Soc. 1960; 82:2731–2735. Synthesis of antihypertensive drug Quinethazone: Englund EE, Neumann S, Eliseeva E, McCoy JG, Titus S, Zheng W, Southall N, Shinn P, Leister W, Thomas CJ, Inglese J, Austin CP, Gershengorn MC, Huang W. MedChemComm. 2011; 2:1016–1020. [PubMed: 22408719] For examples of benzooxazinone, see: Dong G, Wang S, Miao Z, Yao J, Zhang Y, Guo Z, Zhang W, Sheng C. J. Med. Chem. 2012; 55:7593–7613. [PubMed: 22867019] Mueller R, Rachwal S, Lee S, Zhong S, Li Y-X, Haroldsen P, Herbst T, Tanimura S, Varney M, Johnson S, Rogers G, Street LJ. Bioorg. Med. Chem. Lett. 2011; 21:6170–6175. [PubMed: 21889339] Furukawa A, Arita T, Satoh S,

Araki K, Kuroha M, Ohsumi J. *Bioorg. Med. Chem. Lett.* 2009; 19:724–726. [PubMed: 19109017]

- (9). (a) Cheng X, Vellalath S, Goddard R, List B. *J. Am. Chem. Soc.* 2008; 130:15786–15787. [PubMed: 18975905] (b) Rueping M, Antonchick AP, Sugiono E, Grenader K. *Angew. Chem., Int. Ed.* 2009; 48:908–910. (c) Vellalath S, Ori I, List B. *Angew. Chem., Int. Ed.* 2010; 49:9749–9752. (d) Cheng D-J, Tian Y, Tian S-K. *Adv. Synth. Catal.* 2012; 354:995–999. (e) Huang D, Li X, Xu F, Li L, Lin X. *ACS Catal.* 2013; 3:2244–2247. In the reference 9d, *N*-sulfonyl imine was used instead of aldehyde, but the imine was prepared from aldehyde prior to the reaction.
- (10). (a) Testa, B.; Mayer, JM. *Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry, and Enzymology.* Verlag Helvetica Chimica Acta; Zürich, Switzerland: 2003. p. 711–714. (b) Magdalou, J.; Fournel-Gigleux, S.; Testa, B.; Ouzzine, M. *The Practice of Medicinal Chemistry.* 2nd. ed.. Wermuth, CG., editor. Academic Press; London: 2003. p. 517–543.
- (11). Incorporation of fluorine near *O,O*- and *O,N*-ketals showed higher stability than non-fluorinated ketals under acidic condition, see: Bégué JP, Bonnet-Delpon D. *ChemMedChem.* 2007; 2:608–624. [PubMed: 17252616]
- (12). Asymmetric α -fluorination of aldehyde has been reported; however, the resulting α -fluoroaldehydes have not been isolated. Beeson TD, MacMillan DWC. *J. Am. Chem. Soc.* 2005; 127:8826–8828. [PubMed: 15954790] Marigo M, Fielenbach D, Braunton A, Kjærsgaard A, Jørgensen KA. *Angew. Chem., Int. Ed.* 2005; 44:3703–3706. Steiner DD, Mase N, Barbas CF. *Angew. Chem., Int. Ed.* 2005; 44:3706–3710. Brandes S, Niess B, Bella M, Prieto A, Overgaard J, Jørgensen KA. *Chem. - Eur. J.* 2006; 12:6039–6052. [PubMed: 16789058]
- (13). No α -fluoroaldehydes are commercially available because they are unstable due to polymerization. Some α -fluoroacetals (hydrates) are commercially available but in aqueous solution. Instability of α -fluoroaldehydes is described in the following: Davis FA, Kasu PVN, Sundarababu G, Qi H. *J. Org. Chem.* 1997; 62:7546–7547.
- (14). (a) Rauniyar V, Lackner AD, Hamilton GL, Toste FD. *Science.* 2011; 334:1681–1684. [PubMed: 22194571] (b) Phipps RJ, Hiramatsu K, Toste FD. *J. Am. Chem. Soc.* 2012; 134:8376–8379. [PubMed: 22574822] (c) Honjo T, Phipps RJ, Rauniyar V, Toste FD. *Angew. Chem., Int. Ed.* 2012; 51:9684–9688. (d) Phipps RJ, Toste FD. *J. Am. Chem. Soc.* 2013; 135:1268–1271. [PubMed: 23330962] (e) Shunatona HP, Früh N, Wang Y-M, Rauniyar V, Toste FD. *Angew. Chem., Int. Ed.* 2013; 52:7724–7727. (f) Wu J, Wang Y-M, Drljevic A, Rauniyar V, Phipps RJ, Toste FD. *Proc. Natl. Acad. Sci. U. S. A.* 2013; 110:13729–13733. [PubMed: 23922394] (g) Romanov-Michailidis F, Guénée L, Alexakis A. *Angew. Chem., Int. Ed.* 2013; 52:9266–9270. (h) Xie W, Jiang G, Liu H, Hu J, Pan X, Zhang H, Wan X, Lai Y, Ma D. *Angew. Chem., Int. Ed.* 2013; 52:12924–12927. (i) Yang X, Phipps RJ, Toste FD. *J. Am. Chem. Soc.* 2014; 136:5225–5228. [PubMed: 24684209] Reviews of chiral anions in catalysis: Phipps RJ, Hamilton GL, Toste FD. *Nat. Chem.* 2012; 4:603–614. [PubMed: 22824891] Mahlau M, List B. *Angew. Chem., Int. Ed.* 2013; 52:518–533. Brak K, Jacobsen EN. *Angew. Chem., Int. Ed.* 2013; 52:534–561.
- (15). (a) Rowland GB, Zhang H, Rowland EB, Chennamadhavuni S, Wang Y, Antilla JC. *J. Am. Chem. Soc.* 2005; 127:15696–15697. [PubMed: 16277499] (b) Liang Y, Rowland EB, Rowland GB, Perman JA, Antilla JC. *Chem. Commun.* 2007:4477–4479.
- (16). Guo QS, Du DM, Xu J. *Angew. Chem., Int. Ed.* 2008; 47:759–762.
- (17). Substitution of the salicylamide core afforded decreased ee using the optimized conditions.
- (18). For a majority of the substrates, (*R*)-C₈-TRIP showed satisfactory enantioselectivities (21–98% ee). See Table S1 in the Supporting Information for details.
- (19). A decrease in yield was generally observed with decreased reactivity of sterically demanding nucleophiles.
- (20). In the reaction of **2i**, (*R*)-4-Ph-PhDAP also produced high yield and enantioselectivity (90% yield, 97% ee). See the Supporting Information for details.
- (21). See Table S2 in the Supporting Information for details.
- (22). Homogeneous fluoroamination reactions were carried out with selectfluor in acetonitrile solution in the absence of catalyst and base.
- (23). Moderate yields were due to remaining starting materials and other unidentified minor byproducts.

- (24). Fluoroamination of **1s** using (*R*)-C₈TRIP gave the product **2s** with 9:1 dr. Fluoroamination of **1s** and **1u** under homogeneous condition provided the product **2s** and **2u** in 5:2 and 3:1 ratios, respectively. See the Supporting Information for details.

Table 1

Screening of Catalysts for Fluoroamination and Oxyfluorination

entry	X	catalyst	product	yield (%) ^a	ee (%) ^b
1	NH (1e)	(<i>S</i>)-VAPOL PA	<i>ent</i> - 2e	37 ^c	1 ^c
2	NH (1e)	(<i>R</i>)-C ₈ -TRIP	2e	34 ^c	21 ^c
3	NH (1e)	(<i>R</i>)-PhDAP	2e	13 ^c	87 ^c
4	NMe (1f)	(<i>S</i>)-VAPOL PA	2f ^d	59	27
5	NMe (1f)	(<i>R</i>)-C ₈ -TRIP	2f ^d	65	55
6	NMe (1f)	(<i>R</i>)-PhDAP	2f ^d	72	84
7	NMe (1f)	(<i>R</i>)-PhDAPNHTf	2f ^d	58	55
8	O (1l)	(<i>R</i>)-PhDAP	2l	84	55
9	O (1l)	(<i>R</i>)-C ₈ -TRIP	2l	80	36
10	O (1l)	(<i>R</i>)-TRIP	2l	79	17
11	O (1l)	(<i>R</i>)-Taddol PA	2l	92	67
12	O (1l)	(<i>R</i>)-OC _γ DAP	2l	71	98
13	O (1l)	(<i>S</i>)-VANOL PA	<i>ent</i> - 2l	83	34
14	O (1l)	(<i>S</i>)-VAPOL PA	<i>ent</i> - 2l	76	96

^a Isolated yields after chromatography on silica gel.^b Determined by HPLC.^c Yield and ee of dimeric product **2e**.^d The absolute configuration of **2f** was determined by X-ray crystallography.

Table 2

Scope of Amine Nucleophile in Fluoroamination

entry	X	product	yield (%) ^a	ee (%) ^{b,c}
1	Boc (1a)	2a	--	---
2	Ms (1b)	2b	42	5
3	Ts (1c)	2c	39	11
4	Mbs (1d)	2d	59	16
5	Bn (1g)	2g	60	84
6	Cy (1h)	2h	34	94
7	Ph (1i)	2i	90	98
8	4-OMe-Ph (1j)	2j	65	97
9	4-NO ₂ -Ph (1k)	2k	43	95

^aIsolated yields after chromatography on silica gel.^bDetermined by HPLC.^cThe absolute configurations were tentatively assigned by analogy of **2f**.

Table 3

Scope of Fluoroamination

entry	R ¹	product	yield (%) ^a	ee (%) ^{b,c}
1	4-Cl (1m)	2m	84	89
2	5-Me (1n)	2n	78	97
3	5-OMe (1o)	2o	55	94
4	5-F (1p)	2p	93	96
5	5-Cl (1q)	2q	74	97
6	6-F (1r)	2r	84	92

^a Isolated yields after chromatography on silica gel.

^b Determined by HPLC.

^c The absolute configurations were tentatively assigned by analogy with **2f**.

Table 4

Enantio- and Diastereoselective Fluoroamination

entry	R ²	product	(R)-PhDAP		(R)-4-Ph-PhDAP	
			yield (%) ^a	ee (%) ^{b,c}	yield (%) ^a	ee (%) ^{b,c}
1	Ph (1s)	2s	58 ^f	57 ^f	55 ^f	63 ^f
2	Ph (1s)	2s	74	72	42	87
3	4-iPr-Ph (1t)	2t	46	70	49	77
4	4-tBu-Ph (1u)	2u	55	86	40	84
5	2-thienyl (1v)	2v	51 ^g	72 ^g	53 ^g	58 ^g

^a Isolated yields after chromatography on silica gel.

^b Determined by HPLC.

^c The absolute configurations of the aminal stereocenter was assigned by analogy of **2f**. The relative configuration of **2s** was determined by X-ray crystallography.

^d Determined by ¹⁹F-NMR analysis of the crude reaction mixture.

^e Mixture of isomers was used as a solvent.

^f Toluene and 5 Å MS were used instead of the standard condition.

^g 5 Å MS was used instead of the standard condition.