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Palladium-Catalyzed Regioselective Arylation of Imidazo[1,2-*b*][1,2,4]triazine: Synthesis of an $\alpha_{2/3}$-Selective GABA Agonist

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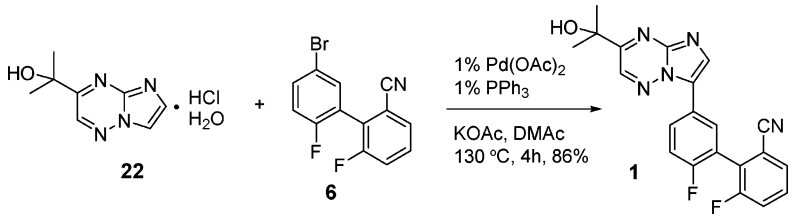

A convergent, practical, and efficient synthesis of 2′,6-difluoro-5′-[3-(1-hydroxy-1-methylethyl)-imidazo[1,2-*b*][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile (**1**), an orally active $GABA_A$ $\alpha_{2/3}$-selective agonist, is described. The seven-step, chromatography-free synthesis was demonstrated on a multikilogram scale and utilized biaryl bromide **6** and imidazotriazine **22** as key intermediates. Biaryl bromide **6** was prepared via a highly selective aromatic bromination. The regioselective condensation of aminotriazine **15** with chloroacetaldehyde provided the desired imidazotriazine intermediate **22**. A highly regioselective palladium-catalyzed arylation in the final step highlights the efficiency of the route.

γ-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter of the central nervous system.[1] Selective ligands for $GABA_A$ receptors,[2] especially those having affinity for the α_2, α_3, and α_5 subunit, are potentially useful in the treatment of adverse conditions affecting the central nervous system such as anxiety, convulsions, and cognitive disorders. The discovery and development of therapeutic agents to treat deficiencies in this field have garnered extensive research efforts.[3] Compound **1**, containing a uniquely functionalized imidazo[1,2-*b*][1,2,4]-triazine core,[4] is an orally active $\alpha_{2/3}$-selective $GABA_A$ agonist possessing promising half-life and suitable oral bioavailability for clinical development.[5] Herein, we report our efforts to design an efficient and practical synthesis to provide bulk quantities of **1** to support extensive biological testing.

Our retrosynthetic strategy for compound **1** is outlined in Scheme 1. Encouraged by recent reports of metal-catalyzed arylations of imidazoles[6] and other electron-rich heteroaromatics,[7,8] we envisioned a highly convergent approach that utilizes a selective Pd-catalyzed arylation of imidazotriazine **22** with biaryl bromide **6**. The imidazotriazine core is derived via annulation of

(1) Sivilotti, L.; Nistri, A. *Prog. Neurobiol*. **1991**, *36*, 35−92.
(2) Bormann, J. *Trends Pharmacol. Sci.* **2000**, *21*, 16−19.
(3) (a) Chambers, M. S.; Atack, J. R.; Broughton, H. B.; Collinson, N.; Cook, S.; Dawson, G. R.; Hobbs, S. C.; Marshall, G.; Maubach, K. A.; Pillai, G. V.; Reeve, A. J.; MacLeod, A. M. *J. Med. Chem.* **2003**, *46*, 2227−2240. (b) Chebib, M.; Johnston, G. A. R. *Clin. Exp. Pharmacol. Physiol.* **1999**, *26*, 937−940. (c) Armer, R. *Curr. Med. Chem.* **2000**, *7*, 199.
(4) Carling, W. R.; Hallett, D. J.; Russell, M. G. N.; Street, L. J. Preparation of 7-phenylimidazo[1,2-*b*][1,2,4]triazines as ligands for GABA receptors. PCT Int. Appl. 2003, 42 pp; WO 2003008418.
(5) Bettati, M.; Blurton, P.; Carling, W. R.; Chambers, M. S.; Hallett, D. J.; Jennings, A.; Lewis, R. T.; Russell, M. G. N.; Street, L. J.; Szekeres, H. J.; Van Niel, M. B. Preparation of 7-phenylimidazo[1,2-*b*][1,2,4]triazines as ligands for GABA receptors. PCT Int. Appl. 2002, 156 pp; WO 2002038568.
(6) (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467−473. (b) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111−3113. (c) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257−272. (d) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274−5275. (e) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 10580−10585.
(7) (a) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951−1958. (b) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677−1680. (c) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301−304. (d) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286−5287. (e) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897−2900.
(8) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835−4837.

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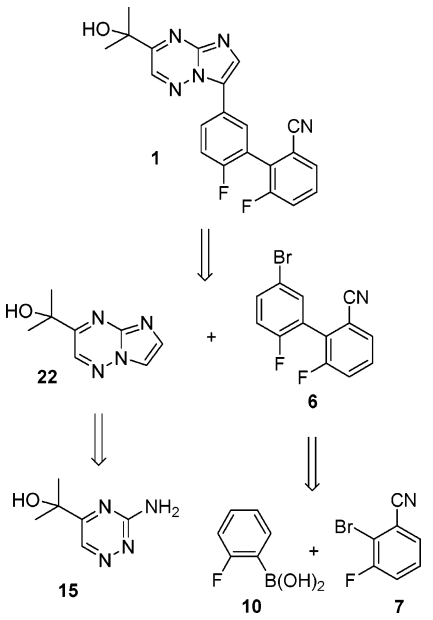
SCHEME 1



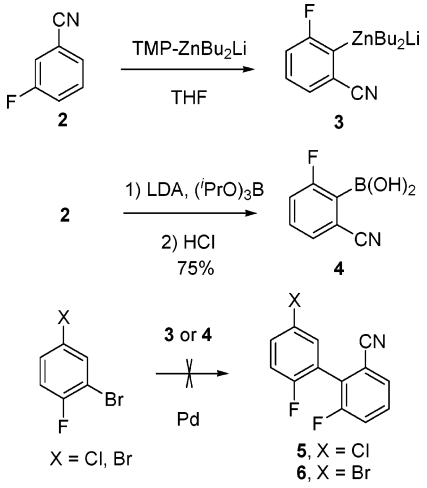
aminotriazine **15**. Biaryl bromide **6** was prepared by means of a Suzuki cross-coupling followed by a regioselective bromination. The synthetic route is a convergent seven-step sequence that relies on a regioselective aminotriazine synthesis to prepare the imidazotriazine core (**22**) and a robust, scaleable synthesis of biaryl bromide **6**.

Results and Discussion

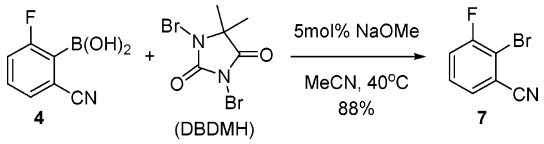
Several synthetic strategies were examined for preparation of biaryl bromide **6**. Our initial approach was to convert 3-fluorobenzonitrile **2** into the nucleophilic component of a transition metal catalyzed cross-coupling reaction.[9] Selective orthometalation of 3-fluorobenzonitrile gave only nitrile addition products with strong bases such as *n*-butyllithium, LDA, or LHMDS, while weaker bases such as Grignard or alkyl zinc halide reagents failed to react. A directed metalation with lithium dialkyl-2,2,6,6-tetramethylpiperidinozincate (TMP-ZnR_2Li), provided aryl-zincate intermediate **3**.[10,11] All attempts to cross-couple aryl-zincate **3**[12] with 2,4-dibromofluorobenzene or iodobenzene were unsuccessful, generally giving no reaction. Varying the alkyl groups of zincate **3** (R = Me, Et, Bu, or *t*-Bu), the amine (TMP or LDA), or the Pd ligand failed to promote the cross-coupling reaction.

Boronic acid **4** was then prepared by adding LDA to a mixture of 3-fluorobenzonitrile and triisopropylborate,[13] followed by acid hydrolysis. Similar to the zincate species **3**, boronic acid **4** failed to provide the desired biaryl product when reacted with 1,3-dibromo-4-fluorobenzene or 2-bromo-4-chlorofluorobenzene under standard Suzuki conditions with a variety of Pd catalysts and ligands. We believe the complete lack of reactivity of zincate **3** and boronic acid **4** toward cross-coupling is due to the electron-withdrawing effects of the aryl substituents.Our next approach was to prepare 2-bromo-3-fluorobenzonitrile **7** and then cross-couple with an appropriate organometallic nucleophile. We previously reported the synthesis of 2-bromo-3-fluorobenzonitrile **7** via treatment of boronic acid **4** with dibromodimethylhydantoin (DBDMH) and found it was essential to conduct the bromodeboronation under slightly basic conditions (Scheme 3).[14] Several cross-coupling partners were explored with bromide **7**, including organometallic reagents **8a**, **8b**, and **8c** which were generated from 2,4-dibromofluorobenzene via a selective metal−halogen exchange reaction with *i*PrMgCl.[15] Unfortunately, Pd-catalyzed reactions of **8a**, **8b**, and **8c** with **7** gave a low yield due to polymerization (Scheme 4). With use of a similar strategy, polymerization was minimized by using organozinc **9**, which was derived from chlorofluorobenzene via selective ortholithi-

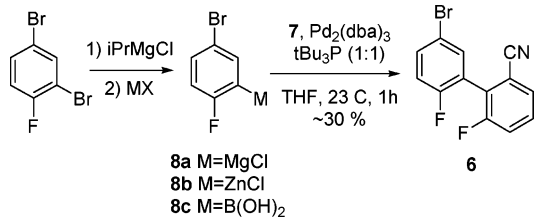
SCHEME 2



SCHEME 3



SCHEME 4



(9) Deiterich, F. *Metal catalyzed cross-coupling reactions*; Wiley-VCH: New York, 1998.

(10) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539−3540.

(11) Confirmation of organozincate formation was established via conversion to bromide **7** with the addition of 5 equiv of Br_2 (75% yield).

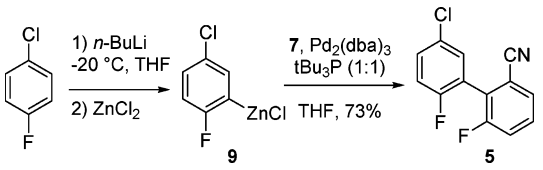
(12) For examples of Pd-catalyzed cross-coupling with zincates, see: Gauthier, D. R., Jr.; Szumigala, R. H., Jr.; Dormer, P. G.; Armstrong, J. D., III; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 375−378.

(13) (a) Kristensen, J.; Lysén, M.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435−1437. (b) Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054−2055. (c) Li, W.; Nelson, D.; Jensen, M.; Hoerrner, R. S.; Cai, D.; Larsen, R.; Reider, P. *J. Org. Chem.* **2002**, *67*, 5394−5397.

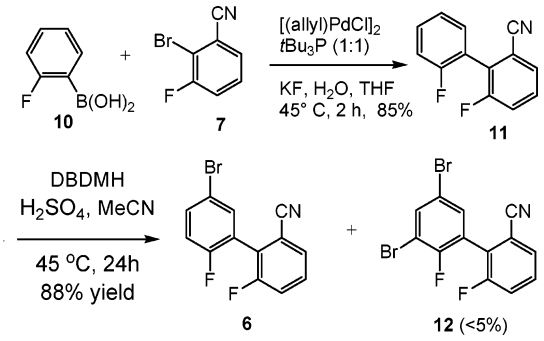
(14) Szumigala, R. H., Jr.; Devine, P. N.; Gauthier, D. R., Jr.; Volante, R. P. *J. Org. Chem.* **2004**, *69*, 566−569.

(15) A sample of Grignard reagent **8a** was quenched with water and a GC assay revealed 20:1 selectivity of 4-bromofluorobenzene versus 2-bromofluorobenzene.

SCHEME 5



SCHEME 6



ation (Scheme 5).[16] Negishi coupling of **7** with organozinc **9** gave a 73% yield of **5**; however, biaryl chloride **5** proved to be a poor penultimate intermediate for the synthesis of compound **1** because the subsequent arylation reaction proceeded in poor yield (vide infra). Thus, biaryl-Br **6** was the desired intermediate and was ultimately prepared via a two-step sequence entailing a Suzuki cross-coupling followed by a highly regioselective aromatic bromination (Scheme 6). Suzuki coupling of boronic acid **10** with bromide **7** gave biaryl **11** in 85% yield. Biaryl **11** was then selectively brominated with Fe (0.5 equiv) and Br_2 (4−6 equiv) in DCE to give biaryl-Br **6** in 75% yield after workup and crystallization from IPA/water.

While the Fe-catalyzed bromination of biaryl-H **11** with Br_2 afforded exclusively the desired bromide in good yield, the reaction was only successful in halogenated solvents and required incremental Br_2 charges during the course of the reaction. Since these reaction requirements were undesirable upon scale-up, alternative bromination conditions were necessary. Treatment of biaryl **11** with *N*-bromosuccinamide[17] (NBS, 1 equiv) or *N*,*N*′-dibromodimethylhydantoin (DBDMH, 0.5 equiv) in the presence of sulfuric or triflic acid[18] (1 equiv) in solvents such as cyclohexane, MeCN, and dichloroethane selectively afforded the desired bromide; however, over brominated products, mainly dibromobiaryl **12** began to form when reactions were maximized for conversion. The combination of DBDMH and H_2SO_4 in MeCN was chosen because the product was conveniently crystallized from the reaction mixture by simply adding H_2O.[19] The amounts of DBDMH and H_2SO_4 were then optimized based upon reaction time, conversion, and minimization of overbrominated products. After treatment of **11** with 1 equiv of H_2SO_4 and 0.6 equiv of DBDMH for 24 h, <5% dibromination occurred and was efficiently removed upon crystallization, providing bromide **6** in 88% yield.

We envisioned accessing the 5-substituted imidazo[1,2-*c*][1,2,4]triazine **22** by performing a regioselective annulation of aminotriazine **15** with chloroacetaldehyde. The aminotriazine **15** precursor could be prepared by a regioselective condensation of aminoguanidine and keto aldehyde **17** or its equivalent. Accordingly, dibromoketone **14**[20] was reacted with aminoguanidine yet the condensation was nonselective, providing an equal mixture of aminotriazines **15** and **16** (Scheme 7). Since the terminal hydrazine nitrogen of aminoguanidine is the most nucleophilic,[21] we anticipated achieving high regiocontrol using keto aldehyde **17**.[22] The aqueous base hydrolysis of dibromide **14** gave an intractable mixture of keto aldehyde **17**, present as a complex hydrate/aldehyde mixture along with several byproducts, which was treated with aminoguanidine bicarbonate providing the desired aminotriazine regioisomer in a 19:1 ratio.[23] However, aminotriazine **15** was isolated in only 28% overall yield from the dibromoketone **14** after a difficult extractive workup. The low yield is attributed to byproducts **18a**, **19a**, and **19b**[24] which were formed during the hydrolysis of dibromide **14**. Reports on the preparation of keto aldehyde **17** from 2-methyl-3-butyn-2-ol or 3-methyl-2-butenone have appeared, yet these oxidations required stoichiometric use of indelible toxic promoters such as SeO_2 or $Hg(OAc)_2$.[25] Ultimately, the keto aldehyde formation was circumvented and aminotriazine **15** was prepared in 65% isolated yield using our recently reported conditions for the regioselective cyclization of aminoguanidine with bis-morpholine ketoaminals **20** (Scheme 8).[26] This strategy takes advantage of an in situ generated N,O-acetal species (**21**) that selectively reacts with aminoguanidine acetate to provide a substantially improved yield of the desired product. Additionally, the isolation of aminiotriazine **15** was now straightforward, simply requiring partial concentration and aging at 0 °C for 1 h. The precipitated product was analytically pure and isolated in an overall 65% yield from dibromide **14**.

Aminotriazine **15** was then treated with chloroacetaldehyde in IPA/H_2O to give imidazotriazine **22** (Scheme 9). The product was extracted from the crude reaction with *i*-BuOH, solvent switched to MeCN via a constant volume distillation, and then conveniently isolated as the HCl salt monohydrate in 73% yield.

Initially, we envisioned the end-game strategy involving a selective bromination of imidazotriazine **22** followed by a Pd cross-coupling reaction with a boronic acid (**23**) generated from biaryl bromide **6** (Scheme 10). While this

(16) Mongin, F.; Schlosser, M. *Tetrahedron Lett.* **1996**, *37*, 6551.

(17) For bromination with NBS in H_2O/H_2SO_4, see: Lambert, F. L.; Ellis, W. D.; Parry, R. J. *J. Org. Chem.* **1965**, *30*, 304−305.

(18) Only strong protic acids affected the desired bromination.

(19) With use of DBDMH, the hydantoin byproduct precipitated during the course of the reaction and subsequently dissolved with the addition of H_2O, whereas the succinamide generated by using NBS inhibited crystallization of the product.

(20) Prepared via bromination of the corresponding methyl ketone, see: (a) Nan'ya, S.; Ishida, H.; Moiji, E. J.; Butsugan, Y.; Bajji, A. C. *J. Heterocycl. Chem.* **1994**, *31*, 401. (b) Boeykens, M.; De Kimpe, N. *Tetrahedron* **1994**, *50*, 12349.

(21) (a) Ueda, T.; Furukawa, M. *Chem. Pharm. Bull.* **1964**, *12*, 100−103. (b) Osman, A. N.; Botros, S.; Kandeel, M. M.; Khalil, N. A.; Abd El-Latif, H. A. *Indian J. Chem.* **1996**, *35B*, 446−455.

(22) Pfuller, O. C.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 8821−8824.

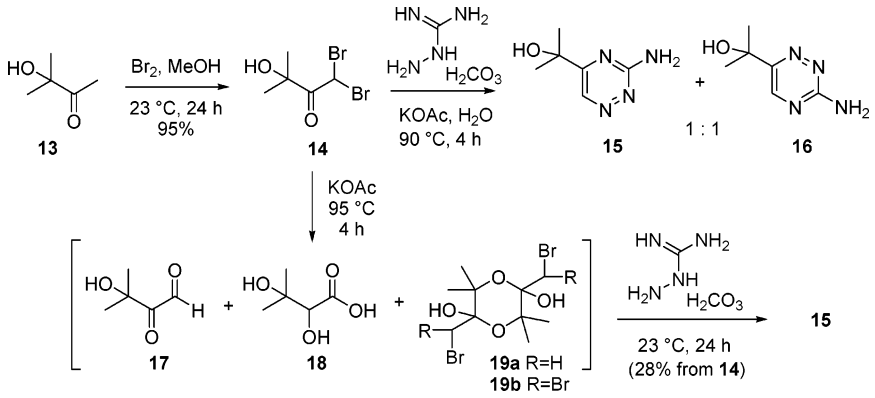
(23) The regioselectivity was found to be highly pH dependent and gave optimal selectivity at pH 8−9.

(24) Cyclic byproduct **19a** was found to be extremely stable to the hydrolysis conditions. Thus, once formed it does not convert back to keto aldehyde **17**.

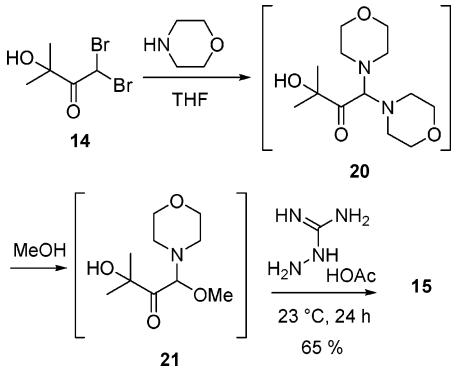
(25) (a) Ballistreri, F. P.; Failla, S.; Tomaselli, G. A. *J. Org. Chem.* **1988**, *53*, 830−831. (b) Colonge, J.; Cumet, L. *Bull. Soc. Chim. Fr. 1947*, 841−843.

(26) Limanto, J.; Desmond, R. A.; Gauthier, D. R., Jr.; Devine, P. N.; Reamer, R. A.; Volante, R. P. *Org. Lett.* **2003**, *5*, 2271−2274.

SCHEME 7



SCHEME 8



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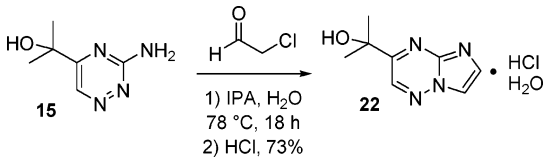
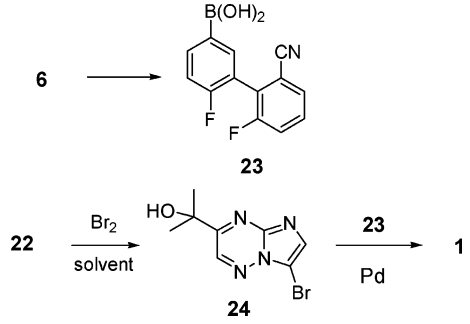


SCHEME 10



route was plausible,[27] a more efficient strategy based upon recent reports of Pd-catalyzed arylation reactions with electron-rich heterocycles, such as oxazoles, imidazoles, thiazoles, furans, and imidazopyrazines, led us to explore the direct coupling of imidazotriazine **22** with biaryl bromide **6**. Similar to the imidazopyrazines,[8] arylation is selective and parallels aromatic bromination, reacting at the sight of the highest nucleophilic character.[28] Electrophilic aromatic substitution appears to be the operative mechanism.[29]

The reaction parameters including Pd source, base, solvent, and additives of the arylation reaction were explored (Table 1). Arylation reactions with biary chloride **5** gave poor conversions even with catalysts that have shown good reactivity with aryl chlorides in metal-catalyzed couplings.[30] For example, Pd(*t*-Bu)$_3$P[31] and Pd/IMes[32] were the only catalysts that produced any product (Table 1, entries 1 and 2). Biaryl bromide **6** was found to be reactive under a wide range of Pd/ligand systems. Although several Pd(0) and Pd(II) sources were effective, $Pd(OAc)_2$ was robust and commercially less expensive compared to other Pd sources. Many phosphine ligands were evaluated, but none were superior to triphenylphosphine in terms of cost and conversion. The Pd/PPh_3 ratio had a significant effect on the reaction and more favorable results were obtained with equal molar amounts of ligand and $Pd(OAc)_2$ (Table 1, entry 4 vs 5).[31] In accord with Miura's initial report with imidazoles, organic amine bases were completely ineffective, while either Cs_2CO_3 or K_2CO_3 afforded much better conversion than the less soluble Li and Na carbonates. High boiling polar aprotic solvents such as DMF, 1,4-dioxane, NMP, and DMAc gave the best conversions probably due the ability to partially dissolve the inorganic base at high temperature. Accordingly, reactions conducted in less polar, high boiling solvents, such as toluene, provided poor conversion (<20%). When imidazotriazine HCl hydrate **22** was extensively dried in a vacuum oven to afford the anhydrous HCl salt, the reaction rate and conversion suffered dramatically. The arylation was optimal with only the water provided by the hydrated intermediate **22**, although having up to 5% water by volume in the reaction medium did not significantly impede the reaction. Initially, our best conditions used 5 mol % of $Pd(OAc)_2$, 5 mol % of PPh_3, and 2 equiv of K_2CO_3 in DMF at 100 °C, where reactions were typically complete in 4 h (entry 5).

(27) Bettati, M.; Chambers, M. S.; Goodacre, S. C.; Hallett, D. J.; Russell, M. G. N.; Street, L. J. Preparation of imidazotriazines as ligands for GABA receptors. PCT Int. Appl. 2003, 67 pp; WO 2003093272.

(28) Imidazotriazine **22** was selectively brominated at the 7-position to give **24** in 75% yield by treatment with NaOAc and Br_2 in HOAc; see ref 5.

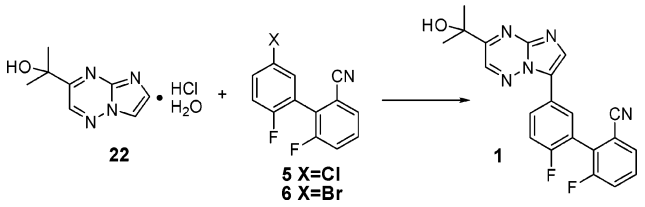
(29) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159−1162.

(30) For an excellent review, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed*. **2002**, *41*, 4176−4211.

(31) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

(32) (a) Arduengo, A. J., III *Acc. Chem. Res.* **1999**, *32*, 913−921. (b) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805.

TABLE 1. Arylation of Imidazotriazine 22



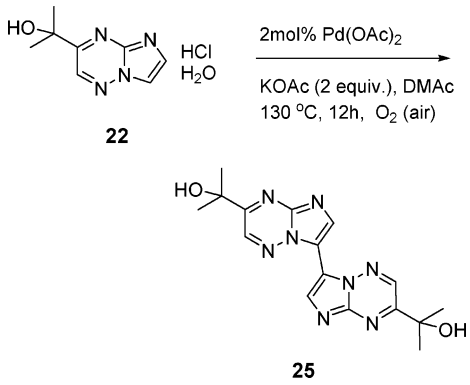
	reaction conditions						
entry	X	solvent	base (equiv)	catalyst/ligand (ratio)	temp, °C	time, h	yield, %
1	Cl	dioxane	Cy_2NMe	5% Pd_2dba_3/*t*-Bu_3P (1:1)	100	48	14
2	Cl	dioxane	Cs_2CO_3	5% Pd/IMes	100	48	20
3	Br	DMF	Cs_2CO_3 (2)	5% $Pd(OAc)_2/PPh_3$ (1:2)	100	4	70
4	Br	DMF	K_2CO_3 (2)	5% $Pd(OAc)_2/PPh_3$ (1:2)	100	4	70
5	Br	DMF	K_2CO_3 (2)	5% $Pd(OAc)_2/PPh_3$ (1:1)	100	4	82
6	Br	DMF	K_2CO_3 (2)	2% $Pd(OAc)_2/PPh_3$ (1:1)	100	24	45
7	Br	DMAc	KOAc (4)	5% $Pd(OAc)_2/PPh_3$ (1:1)	100	24	88
8	Br	DMAc	KOAc (4)	1% $Pd(OAc)_2/PPh_3$ (1:1)	130	36	85
9	Br	DMAc	KOAc (2.5)	1% $Pd(OAc)_2/PPh_3$ (1:1)	130	4	86

Although these conditions were robust, a lower catalyst loading could not be tolerated (entry 6, reaction stalled at 50% conversion, 45% yield). Switching the base to KOAc (4 equiv) gave a slower reaction with 5 mol % of catalyst (entry 7), but catalyst loading could be reduced to 2 mol % when run at 130 °C for 36 h in DMAc (entry 8). Temperatures over 100 °C in DMF could not be tolerated due to debromination of **6** generating **11** as the major product. Significant rate effects were observed by varying the amount of KOAc, the only base that was completely soluble under the reaction conditions. At least 2 mol of base are necessary to arylate the imidazotriazine HCl salt (**22**), but excess KOAc apparently retards the rate while still maintaining an active catalyst. For example, the optimal arylation conditions were found by reducing the amount of KOAc from 4 to 2.5 equiv, yielding an 86% yield in only 4 h vs 36 h (Table 1, compare entries 8 and 9).

The arylation reaction produced only two significant side products, biaryl **11** and imidazotriazine dimer **25**, both formed in <3%. We presumed that the dimerization occurs via bis arylation of a Pd(II) species followed by reductive elimination to give **25**. When imidazotriazine **22** was heated with catalyst in the absence of the aryl bromide **6**, only a trace of dimer **25** formed after 24 h at 130 °C. When the same reaction was exposed to atmospheric oxygen, **22** was quantitatively converted to dimer **25** after 12 h (Scheme 11).

The high convergence achieved by using the arylation reaction in the final synthetic step came with the burden of removing the palladium, a necessity required for the preparation of an active pharmaceutical ingredient (API).[33] Although Pd-catalyzed processes are ubiquitous in the literature, only few reports have addressed this problem of removing the residual metal because palladium-catalyzed reactions are typically avoided in the final step toward an API.[34] Indeed, we were disappointed to find

SCHEME 11



that compound **1** has a particularly high affinity toward Pd since standard workup and crystallization procedures gave nominal rejection (e.g., 2500 ppm of Pd with 1 mol % of $Pd(OAc)_2$). The use of immobilized palladium catalysts such as Pd/C[35] resulted in extensive leaching since the isolated product contained >1000 ppm of Pd. Chemical additives such as *n*-Bu_3P[36] and trimercaptotriazine[37] or even high-throughput screening processes[38] with adsorbents such as activated carbon, diatomaceous earth, and immobilized phosphine ligands on polymer supports did not adequately reduce the Pd levels. Fortuitously, crude **1** containing up to 8000 ppm of Pd was recrystallized in EtOH and the resulting **1**·EtOH solvate contained <20 ppm of Pd. Apparently the affinity for Pd greatly diminishes when EtOH enters the crystalline

(33) Only a few parts per million of a heavy metal such as palladium can be tolerated in an API according to the guidelines of the International Conference on Harmonization (ICH).

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lattice. A final recrystallization from THF/heptane provided the unsolvated $GABA_A$ agonist **1** in high purity.

Conclusion

We have developed a convergent, practical, and efficient synthesis of a GABA agonist using the crystalline intermediates biaryl bromide **6** and imidazotriazine **22**. Biaryl bromide **6** was prepared via a highly selective aromatic bromination with DBDMH and H_2SO_4. The regioselective condensation of aminotriazine **15** with chloroacetaldehyde provided the desired imidazotriazine intermediate **22** as the HCl hydrate salt. In the final step, imidazotriazine **22** was selectively arylated under palladium-catalyzed conditions, and a simple recrystallization of **1** as the EtOH solvate effectively removed the homogeneous palladium allowing the API to be acceptable for human clinical trials. The seven-step, chromatography-free synthesis was demonstrated on a multikilogram scale.

Experimental Section

General. Solvents and common reagents were purchased from a commercial source and used without purification. All reactions were conducted under N_2 atmosphere with standard air-free manipulation techniques. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer and chemical shifts are reported in ppm downfield from tetramethylsilane (TMS). High Performance Liquid Chromatography (HPLC) analysis was performed with a YMC-Pack Pro C18 (250 × 4.6 mm i.d.) column under the following conditions: 80% MeCN:20% 0.1% vol H_3PO_4 in H_2O mobile phase, 1 mL/min flow rate, 210 nm wavelength detection, 35 °C column temperature. Melting points are uncorrected. All new compounds are fully characterized below.

(2-Cyano-6-fluorophenyl)boronic Acid (4). To a 100-L round-bottom flask equipped with an overhead stirrer, thermocouple, and N_2 inlet was added **2** (4.00 kg, 33.03 mol), $B(OiPr)_3$ (6.50 kg, 34.7 mol), and THF (20 L). The solution was cooled to −20 °C and a 1.8 M LDA solution in heptane/THF/ethylbenzene (18.7 L, 33.7 mol) was added to the solution over ∼1 h with the internal temperature maintained at <5 °C. The reaction was aged for 15 min at 0 °C and assayed for completion by HPLC. The reaction was quenched into a 0−5 °C mixture of 5 N HCl (26 L) and MTBE (20 L) over 30 min. The resulting mixture was agitated for 30 min at 23 °C. Upon settling, the aqueous layer was cut and back-extracted with MTBE (20 L). The organic layers were combined and washed with a 20 wt % brine/2.5 wt % $KHCO_3$ wash (17 L). The organic solution was concentrated under vacuum to approximately 10 L and a constant volume solvent switch was performed: MeCN (∼20 L) was continuously added to the MTBE/THF solution of boronic acid with the volume maintained at approximately 10 L (temperature maintained <30 °C, 20 to 28 in. Hg). After solvent switch to MeCN, the water concentration was 2.5−5.0% as determined by Karl Fisher titration. The solution of **4** (4.08 kg, 75% yield) in MeCN was taken directly into the next reaction without further manipulation.

2-Bromo-3-fluorobenzonitrile (7). To a 100-L round-bottom flask equipped with an overhead stirrer, thermocouple, and N_2 inlet was added a solution of **4** (3.56 kg, 21.6 mol) in MeCN. The solution was cooled to 15 °C and 25% NaOMe in MeOH (247 mL, 1.10 mol) was added. In a separate vessel, a slurry of DBDMH (1,3-dibromo-5,5-dimethylhydantoin, 6.79 kg, 23.7 mol) in MeCN (18 L) was prepared. Approximately 10−15% of the DBDMH slurry was transferred to the boronic acid solution with the temperature maintained between 15 and 25 °C. The reaction was aged for 15 min during which an exotherm occurred indicating reaction initiation. The remaining slurry of DBDMH was added over 1−2 h with the temperature maintained between 15 and 25 °C. The reaction was aged for 1 h after all DBDMH was added. The reaction was cooled to 5−10 °C, quenched with 20% Na_2SO_3 (18 L), and diluted with MTBE (18 L). Upon agitating and settling, the aqueous layer was cut and the organic layer was washed with 1 N NaOH (36 L). The MTBE solution of **7** was assayed for yield by HPLC (3.80 kg, 88% yield).

5′-Chloro-2′,6-difluorobiphenyl-2-carbonitrile (5). To a −40 °C solution of 4-chlorofluorobenzene (10.0 mmol) in dry THF (13.0 mL) was added hexyllithium (2.5 M in hexane; 11.0 mmol) with the temperature maintained at <−20 °C. The reaction was aged for 1 h at −20 to −25 °C. Anhydrous zinc chloride (∼1.5 M in THF; 11.0 mmol) was slowly added to the aryllithium with the temperature maintained at <0 °C. Upon aging for 30 min at 0 °C, the mixture was degassed (five vacuum/N_2 purges) and $Pd_2(dba)_3$ (0.125 mmol), t-Bu_3P (0.25 mmol), and **7** (10.0 mmol) were added sequentially to the reaction mixture. The reaction warmed to 23 °C and was aged for 1 h. After aqueous workup (10% brine; 2 × 10 mL), **5** was isolated as a white solid in 73% yield after silica gel chromatography. Mp 107−110 °C; IR (KBr pellet) 3080, 2923, 2854, 2237, 1496, 1456, 1260, 1217, 962, 819, 799 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, J = 7.7 Hz, 1H), 7.53 (dt, J = 8.0, 5.2 Hz, 1H), 7.48−7.39 (m, 3H), 7.19 (t, J = 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2 (J_{CF} = 136.3 Hz), 157.7 (J_{CF} = 134.5 Hz), 131.4 (J_{CF} = 8.6 Hz), 131.3, 130.9 (J_{CF} = 8.9 Hz), 129.4 (J_{CF} = 3.3 Hz), 129.1 (J_{CF} = 3.9 Hz), 125.7 (J_{CF} = 19.5 Hz), 120.7 (J_{CF} = 17.7 Hz), 120.6 (J_{CF} = 22.5 Hz), 117.4 (J_{CF} = 23.8 Hz), 116.3 (J_{CF} = 4.0 Hz), 114.9 (J_{CF} = 4.2 Hz); ^{19}F NMR ($CDCl_3$, 376.4 MHz) −110.6 (J_{FF} = 10.3 Hz), −116.3 (J_{FF} = 8.9 Hz). $C_{13}H_6ClF_2N$ required: C, 62.54; H, 2.42; N, 5.61. Found: C, 62.82; H, 2.29; N, 5.38.

2′,6-Difluoro-1,1′-biphenyl-2-carbonitrile (11). 2-Fluorophenylboronic acid **10** (3.0 kg, 21.4 mol) and K_3PO_4 (4.0 kg, 18.7 mol) were added to a solution of THF (25.5 L) and water (8.5 L). The resulting mixture was thoroughly degassed via vacuum/N_2 purges (5 times). A solution of 10% tri-*tert*-butylphosphine in hexanes (1.3 L, 0.42 mol) was added to the reaction, followed by allylpalladium chloride dimer (77.7 g, 0.21 mol). A solution of bromobenzonitrile **7** (3.4 kg, 17.0 mol) in MeCN (18 L) was slowly added to the reaction over 1 h to control the exotherm. The reaction was aged for 2 h at 45−50 °C, cooled to 5 °C, and quenched with 1 N NaOH (17.0 L). The biphasic mixture was vigorously agitated for 15 min and transferred to an extraction vessel. The aqueous layer was cut upon settling. The organic layer was sequentially washed with 1 N NaOH (17.0 L) and then saturated brine (17.0 L). The crude organic solution of **11** was assayed at 90% yield by HPLC, using an analytically pure standard as reference. The solution of **11** in THF was converted over to a solution in IPA via a constant volume distillation (17.0 L, 5 mL/g vs assay yield of **11**). The resulting slurry was heated to 50 °C for 30 min to dissolve all solids. The solution was allowed to slowly cool to 23 °C. To the resulting slurry was added water (17.0 L) over 1 h and the mixture was cooled to 0−5 °C. The slurry was filtered and the filter-cake was washed with a 5 °C 1:1 IPA/water solution (10.2 L). The solids were dried under a N_2 stream for 12 h and then in a vacuum oven at 40 °C to remove any remaining water. Biaryl **11** was isolated as a white solid (3.53 kg, 88.0 wt %, 85% yield) with 96.3% purity by HPLC. An analytically pure sample of **11** was obtained by recrystallization from 1:1 IPA/H_2O then dried in a vacuum oven. Mp 75−75.5 °C; IR (thin film) 3085, 2231, 1615, 1603, 1583, 1569, 1080, 1039, 1008, 983, 919 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, J = 7.6 Hz, 1H), 7.53−7.41 (m, 4H), 7.32−7.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.9 (J_{CF} = 7.3 Hz), 158.4 (J_{CF} = 5.9 Hz), 131.5 (J_{CF} = 8.2 Hz), 130.3 (J_{CF} = 8.8 Hz), 129.0 (J_{CF} = 3.7 Hz), 127.2 (J_{CF} = 20.1 Hz), 124.3 (J_{CF} = 3.5 Hz), 120.4 (J_{CF} = 22.8 Hz), 119.2 (J_{CF} = 15.7 Hz), 116.7 (J_{CF} = 4.0 Hz), 115.9 (J_{CF} = 21.7 Hz), 114.9 (J_{CF} = 4.6 Hz); ^{19}F NMR ($CDCl_3$, 376.4 MHz) −110.8 (J_{FF} = 10.8 Hz), −113.8 (J_{FF} =

10.5 Hz). $C_{13}H_7F_2N$ required: C, 72.56; H, 3.28; N, 6.51. Found: C, 72.40; H, 3.25; N, 6.41.

5′-Bromo-2′,6-difluorobiphenyl-2-carbonitrile (6). To a round-bottom flask equipped with a condenser under N_2 was added solid biaryl **11** (3.31 kg, 15.39 mol) and acetonitrile (24.8 L). The solution of **11** in MeCN should have <5000 ppm water by Karl Fisher titration to achieve an efficient transformation. To this solution was added solid DBDMH (4.4 kg, 15.39 mol) in one portion at room temperature to give a yellow-orange suspension. The addition of DBDMH is endothermic, which brings the batch temperature to about 10−13 °C. Concentrated sulfuric acid (1.28 L, 23.08 mol) was then added slowly over 15−20 min to give a turbid solution, which was then heated to 45 °C and aged for 12 h. The reaction was monitored by HPLC and a 98% conversion was typically obtained after 12 h. At the end of the reaction, water (24.8 L) was slowly added over 1.5 h to the cloudy reaction mixture while maintaining the internal temperature at 45−50 °C. Addition of the first 5% of H_2O results in a 10−15 °C exotherm. During addition of the first half of H_2O, the reaction mixture turns from orange cloudy to a clear red solution, after which the desired product begins to precipitate. Vigorous stirring is usually required to ensure homogeneous crystallization. At the end of the H_2O addition, the resulting suspension was allowed to cool to room temperature (20−23 °C), aged for 3 h, and then filtered. The filter cake was then washed with 1:1 MeCN:H_2O (24.8 L) and dried in vacuo under a stream of N_2. Biaryl bromide **6** was isolated as a white crystalline solid in 88% yield (3.98 kg). Mp 130−131 °C; IR (thin film) 3048, 2238, 1603, 1563, 1290, 1162, 1121, 1020, 980, 838, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62−7.50 (m, 4H), 7.44 (dt, J = 9.2, 1.2 Hz, 1H), 7.14 (t, J = 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4 (J_{CF} = 80.4 Hz), 157.9 (J_{CF} = 79.1 Hz), 134.4 (J_{CF} = 8.2 Hz), 134.1, 130.9 (J_{CF} = 8.8 Hz), 129.1 (J_{CF} = 3.9 Hz), 125.6 (J_{CF} = 19.7 Hz), 121.2 (J_{CF} = 17.2 Hz), 120.6 (J_{CF} = 22.5 Hz), 117.8 (J_{CF} = 23.4 Hz), 116.6 (J_{CF} = 3.8 Hz), 116.3 (J_{CF} = 4.0 Hz), 114.9 (J_{CF} = 4.2 Hz); ^{19}F NMR ($CDCl_3$, 376.4 MHz) −110.6 (J_{FF} = 10.2 Hz), −115.7 (J_{FF} = 10.3 Hz). $C_{13}H_6BrF_2N$ required: C, 53.09; H, 2.06; N, 4.76. Found: C, 53.01; H, 1.77; N, 4.53.

2-(3-Amino-1,2,4-triazin-5-yl)propan-2-ol (15). Formation of aminal and *N*,*O*-acetal intermediates: To a solution of 1,1-dibromo-3-hydroxy-3-methyl-2-butanone (9.71 kg, 37.35 mol) in THF (48 L) under N_2 at 45 °C was slowly added neat morpholine (13.4 L, 53.15 mol) over a period of 4 h. The resulting suspension was then heated to 66−68 °C and aged for 18 h. The reaction was monitored by ^1H NMR spectroscopy and judged complete when ≥97% conversion was obtained. The yellow suspension was then cooled to room temperature and filtered. The wet filter-cake obtained (i.e., morpholine hydrobromide salt) was washed with THF (38 L) and the combined filtrate was then concentrated under a partial vacuum (5−10 Torr, pot temperature =15−20 °C) and solvent switched to MeOH with a final volume of 25 L.

Preparation of aminoguanidine acetate solution: To a suspension of aminoguanidine bicarbonate (5.08 kg, 37.35 mol) in MeOH (25 L) under N_2 at 25 °C was slowly added neat AcOH (6.4 L, 112.06 mol) over a period of 1 h. The resulting white suspension was then aged at room temperature for 4−12 h, after which the CO_2 evolution would cease and a thin suspension was typically obtained.

Cyclization−aminotriazine formation: To the MeOH solution of aminal/*N*,*O*-acetal intermediates obtained above was slowly added the pre-made solution of aminoguanidine acetate at room temperature over a period of 1 h. The resulting solution was then heated to 67 °C and aged for 14 h. At the end of the reaction, the dark brown solution was cooled to room temperature and concentrated to about half its volume (25−28 L). An equal volume of H_2O (28 L) was added, followed by heptane (15 L). The resulting biphasic layers were stirred vigorously for 0.5 h and the aqueous layer was separated. The MeOH/H_2O solution was then concentrated to half its volume (28 L), after which the desired aminotriazine regioisomer begins to precipitate. The resulting suspension was then cooled to 3−5 °C and aged for 6−12 h. The suspension was filtered and the wet cake was washed with cold H_2O (10−14 L). The yellowish solid was then dried overnight in vacuo at 25−35 °C under a stream of N_2 to afford 3.74 kg (65% yield) of **15** in ≥99.5% regioisomeric ratio.

2-Imidazo[1,2-*b*][1,2,4]triazin-3-ylpropan-2-ol Hydrochloride Hydrate (22). To a solution of aminotriazine **15** (2.00 kg, 12.97 mol) in isobutanol (16 L) was added 50 wt % aqueous chloroacetaldehyde (5 L, 39.00 mol). The reaction was warmed to 85 °C and the resulting dark mixture was aged at 85 °C for 22 h. The reaction was cooled to room temperature and water (16 L) was added. The layers were mixed and separated. The acidic water solution containing the imidazotriazine was made basic (pH 8−9) with 50% NaOH and extracted with EtOAc (3 × 16 L). The EtOAc solution of the imidazotriazine was distilled and solvent switched to acetonitrile. To the acetonitrile solution of **22** was added 1.1 equiv of conc HCl over 1 h and the resulting slurry was aged for 4 h at 0−3 °C. The solid was isolated by filtration and the cake was washed with cold acetonitrile. The solid was air-dried to give 1.76 of kg imidazotriazine−HCl salt (60% yield). The solid typically contained ∼5% water. A sample was further dried in a vacuum oven to give anhydrous **22** as an off-white solid. Mp 225−230 °C dec; IR (thin film) 3245, 3124, 3068, 2982, 2849, 2779, 1730, 1561, 1523, 1503, 1456, 1400, 1139, 1275, 1003, 800 cm^{-1}; ^1H NMR (d_6-DMSO, 400 MHz) δ 9.34 (s, 1H), 8.63 (s, 1H), 8.35 (s, 1H), 7.90−7.00 (br s, 2H), 1.55 (s, 6H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 167.4, 141.1, 139.0, 126.2, 116.5, 72.5, 29.5. HRMS for $C_8H_{11}N_4O$ (179.0933) found 179.0975. $C_8H_{11}ClNO$ required: C, 44.76; H, 5.17; N, 26.10. Found: C, 44.48; H, 4.98; N, 25.78.

2′,6-Difluoro-5′-[3-(1-hydroxy-1-methylethyl)imidazo-[1,2-*b*][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile (1). To a 72-L round-bottom flask under N_2 is added imidazotriazine **22** (2.21 kg, 10.29 mol), biaryl bromide **6** (2.75 kg, 9.35 mol), KOAc (2.29 kg, 23.4 mol), $Pd(OAc)_2$ (31.5 g, 0.140 mol), PPh_3 (36.8 g, 0.140 mol), and DMAc (22.1 L). The slurry was warmed to 130 °C and the near homogeneous dark solution was aged at 130 °C until >90% conversion. After 4 h, the solution was cooled to 80 °C and H_2O (4.42 L) and Darco G-60 (1.1 kg) were added. The resulting slurry was aged at 60 °C for 1 h then filtered through solka floc at 60 °C. The filter-cake was washed with 5:1 DMAc/H_2O (13.3 L). The combined filtrate and wash was warmed to 100 °C and water (17.7 L) was added while maintaining the temperature at >90 °C. The resulting solution is seeded at 90−95 °C with a sample of crystalline **1** (0.5%, 168.0 g). To the resulting thin slurry was added H_2O (14.6 L) over 1 h at 90−95 °C. The resulting slurry was aged 1 h at 90−95 °C, then cooled to 20−25 °C over 2 h before filtering. The batch was filtered and the filter-cake was washed with 1:1 DMAc/H_2O (13.8 L) and then H_2O (13.8 L) and dried in a vacuum oven set at 80 °C, 130 Torr. **1** was isolated (3.15 kg, 86% yield) as a mustard yellow solid contaminated with 4500 ppm Pd.

2′,6-Difluoro-5′-[3-(1-hydroxy-1-methylethyl)imidazo-[1,2-*b*][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile−Ethanol (1:1) (1·EtOH solvate). Crude **1** (2.50 kg, 6.38 mol) was slurried in absolute EtOH (82.5 L) and warmed to reflux. After all solids were dissolved, the solution was slowly cool to 20−25 °C. The EtOH solvate precipitates during the cool-down period. The slurry was concentrated to 25 L under vacuum with a temperature <25 °C. The slurry was aged for 1 h at 23 °C and then filtered. The filter-cake was washed with EtOH (14 L) and then dried in a vacuum oven set at 60 °C with a nitrogen purge (23 "Hg). **1**·EtOH solvate was isolated as a bright yellow solid in 93% yield (2.60 kg) and contained <20 ppm Pd. Mp 120−122 °C; IR (thin film) 3201, 2974, 2236, 1592, 1571, 1545, 1513, 1497, 1411, 1313, 987, 917, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.85 (s, 1H), 8.19 (s, 1H), 8.14−8.09 (m, 2H), 7.64 (dd, J = 8.3, 0.7 Hz, 1H), 7.54 (dt, J = 8.1, 5.0 Hz, 1H), 7.46 (dt, J = 8.6, 1.1 Hz, 1H), 7.36 (t, J = 8.8 Hz,

1H), 4.04 (s, 1H), 3.71 (dt, J = 11.7, 7.0 Hz, 2H), 1.69 (s, 6H), 1.23 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.8 (J_{CF} = 39.5 Hz), 159.3, 158.3 (J_{CF} = 40.7 Hz), 141.6, 136.2, 133.7, 130.7 (J_{CF} = 7.2 Hz), 129.6, 129.5, 129.2 (J_{CF} = 3.7 Hz), 126.5 (J_{CF} = 19.7 Hz), 125.1, 124.3 (J_{CF} = 3.9 Hz), 120.6 (J_{CF} = 22.3 Hz), 119.9 (J_{CF} = 16.6 Hz), 116.8, 116.5, 114.9 (J_{CF} = 4.3 Hz), 72.6, 58.2, 29.6, 18.3; ^{19}F NMR ($CDCl_3$, 376.4 MHz) −111.4 (J_{FF} = 12.1 Hz), −112.9 (J_{FF} = 10.9 Hz). HRMS for $C_{21}H_{16}F_2N_5O$ (392.1323) found 392.1329. $C_{23}H_{21}F_2N_5O_2$ required: C, 63.15; H, 4.84; N, 16.01. Found: C, 62.82; H, 4.52; N, 16.02.

2′,6-Difluoro-5′-[3-(1-hydroxy-1-methylethyl)imidazo-[1,2-*b*][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile (1). 1·EtOH solvate (2.00 kg, 4.57 mol) was slurried in THF (60 L) and warmed to 30 °C. The cloudy solution was transferred to a separate vessel via a 1 μm line filter to remove the precipitated imidazotriazine dimer **25**. The resulting solution was concentrated under vacuum at <25 °C to 20 L. A slurry forms during the concentration, and the resulting slurry was aged at 20−22 °C for 0.5−1 h. Heptane (20 L) was added over 1−2 h and then the slurry was aged for 1 h at 20−22 °C. The slurry was filtered, washed with 1:1 THF:heptane (4 L), and then dried under a stream of nitrogen for 15 h. Pure **1** was isolated as a bright yellow solid (1.9 kg, 95% yield). Mp 223−224 °C; IR (thin film) 3302, 2238, 1577, 1509, 1392, 1273, 1001, 990, 747, 717 cm^{-1}; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 9.03 (s, 1H), 8.49 (s, 1H), 8.41−8.34 (m, 2H), 7.91 (dd, J = 7.4, 1.2 Hz, 1H), 7.82−7.72 (m, 2H), 7.62 (t, J = 9.3 Hz, 1H), 5.78 (s, 1H), 1.56 (s, 6H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 160.7, 160.3 (J_{CF} = 61.0 Hz), 157.9 (J_{CF} = 62.1 Hz), 142.0, 137.5, 134.4, 132.3 (J_{CF} = 9.0 Hz), 130.2 (J_{CF} = 3.4 Hz), 129.9 (J_{CF} = 8.5 Hz), 129.7, 126.0 (J_{CF} = 20.0 Hz), 125.2 (J_{CF} = 3.4 Hz), 124.2, 121.7 (J_{CF} = 22.3 Hz), 119.9 (J_{CF} = 16.6 Hz), 117.0 (J_{CF} = 11.0 Hz), 116.9 (J_{CF} = 7.3 Hz), 114.4 (J_{CF} = 4.2 Hz), 72.3, 29.7; ^{19}F NMR (d_6-DMSO, 376.4 MHz) −111.9 (J_{FF} = 8.7 Hz), −115.0 (J_{FF} = 9.2 Hz). HRMS for $C_{21}H_{16}F_2N_5O$ (392.1323) found 392.1329. $C_{21}H_{15}F_2N_5O$ required: C, 64.45; H, 3.86; N, 17.89. Found: C, 64.20; H, 3.66; N, 17.82.

2,2′-(7,7′-Biimidazo[1,2-*b*][1,2,4]triazine-3,3′-diyl)dipropan-2-ol (25). Yellow solid isolated from filtration of **1** in THF. Mp 360−362 °C; IR (thin film) 3218, 3129, 2980, 2020, 1528, 1315, 1188, 1147, 1097, 960, 929, 849, 782 cm^{-1}; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 9.12 (s, 2H), 8.74 (s, 2H), 5.82 (br s, 2H), 1.58 (s, 12H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 161.4, 141.6, 138.1, 133.5, 115.8, 72.4, 29.7. HRMS for $C_{16}H_{19}N_8O_2$ (355.1631) found 355.1637. $C_{16}H_{18}N_8O_2$ required: C, 54.23; H, 5.12; N, 31.62. Found: C, 54.64; H, 4.81; N, 31.58.

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