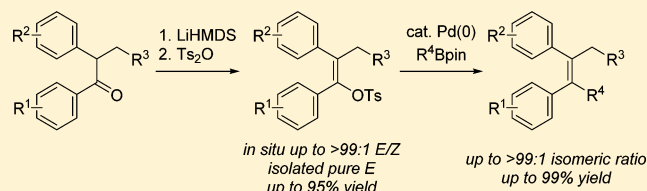


Highly Stereoselective Synthesis of Tetrasubstituted Acyclic All-Carbon Olefins via Enol Tosylation and Suzuki–Miyaura Coupling

Beryl X. Li,[†] Diane N. Le,[†] Kyle A. Mack,[‡] Andrew McClory,[†] Ngiap-Kie Lim,[†] Theresa Cravillon,[†] Scott Savage,[†] Chong Han,[†] David B. Collum,[‡] Haiming Zhang,^{*,†} and Francis Gosselin^{*,†}[†]Small Molecule Process Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, United States[‡]Baker Laboratory, Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853-1301, United States

Supporting Information

ABSTRACT: A highly stereocontrolled synthesis of tetrasubstituted acyclic all-carbon olefins has been developed via a stereoselective enolization and tosylate formation, followed by a palladium-catalyzed Suzuki–Miyaura cross-coupling of the tosylates and pinacol boronic esters in the presence of a Pd(OAc)₂/RuPhos catalytic system. Both the enol tosylation and Suzuki–Miyaura coupling reactions tolerate an array of electronically and sterically diverse substituents and generate high yield and stereoselectivity of the olefin products. Judicious choice of substrate and coupling partner provides access to either the *E*- or *Z*-olefin with excellent yield and stereochemical fidelity. Olefin isomerization was observed during the Suzuki–Miyaura coupling. However, under the optimized cross-coupling reaction conditions, the isomerization was suppressed to <5% in most cases. Mechanistic probes indicate that the olefin isomerization occurs via an intermediate, possibly a zwitterionic palladium carbenoid species.



INTRODUCTION

Tetrasubstituted acyclic all-carbon olefins have attracted tremendous attention owing to their unique structural, physical, and electronic properties.¹ For example, they have been explored extensively for their potential use in molecular devices and liquid crystals² and are widely present in biologically active compounds such as the anticancer agents tamoxifen,³ idoxifene,⁴ and etacstil,⁵ as well as the selective estrogen receptor degrader GDC-0810, which binds to the estrogen receptor and causes it to be degraded and thus downregulated (Figure 1).⁶ Moreover, stereodefined tetrasubstituted olefins are the foundation for numerous asymmetric reactions such as dihydroxylation,⁷ epoxidation,⁸ and hydrogenation⁹ to stereospecifically establish vicinal sp³-hybridized carbon centers.

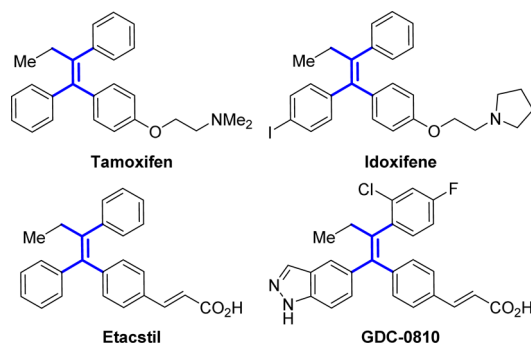


Figure 1. Biologically active compounds containing stereodefined tetrasubstituted olefins.

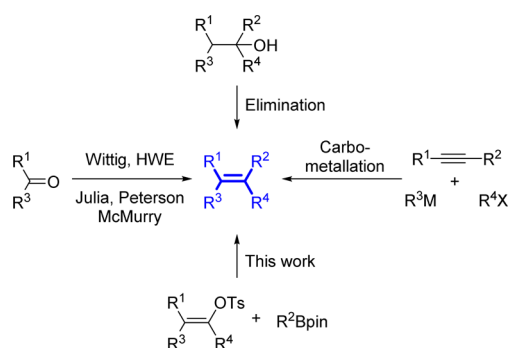
Consequently, a wide variety of synthetic strategies to construct tetrasubstituted acyclic all-carbon olefins have been developed.^{10,11} Classical synthetic methods including Wittig,¹² Horner–Wadsworth–Emmons (HWE),¹² Julia,¹³ Peterson,¹⁴ and McMurry¹⁵ reactions generally afford poor stereoselectivities. Eliminations of highly functionalized tertiary alcohols produce tetrasubstituted olefins;¹⁶ however, the synthesis of the alcohol precursors is often challenging, and multiple elimination pathways frequently result in erosion of stereocontrol.¹⁶ Carbometallation of internal alkynes is commonly employed but suffers from chronic lack of regiocontrol and functional group tolerance (Scheme 1).¹⁷ Recent alternative approaches using Lewis-acid-based electrophiles to activate internal alkynes followed by further functionalization are limited by combinations of harsh reaction conditions, expensive reagents, and poor regioselectivities.¹⁸ Therefore, the development of a general, operationally simple, scalable, highly regio- and stereoselective preparation of tetrasubstituted acyclic all-carbon olefins, while a daunting challenge, will provide a useful new tool for synthetic organic chemists.

In support of our clinical and commercial development of GDC-0810, we were tasked to develop a highly efficient and stereoselective synthesis of tetrasubstituted acyclic all-carbon olefins. Herein we report a highly viable method based on stereoselective enol tosylate formation and subsequent Suzuki–Miyaura coupling (Scheme 2).

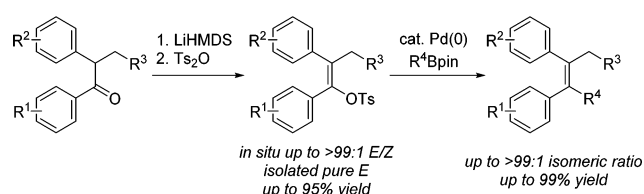
Received: May 16, 2017

Published: July 17, 2017

Scheme 1. Selected Strategies to Prepare Tetrasubstituted Olefins

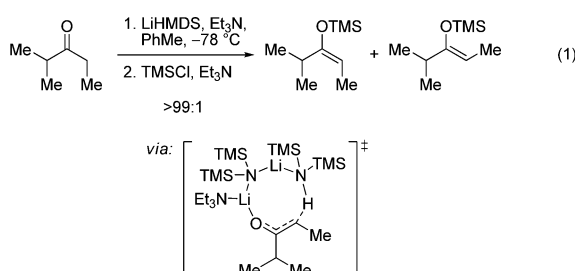


Scheme 2. Stereoselective Olefin Synthesis via Enol Tosylate Formation and Suzuki–Miyaura Coupling



RESULTS AND DISCUSSION

We initiated our studies by investigating the enolization and tosylate formation of commercially available 1,2-diphenylbutan-1-one (**1a**) by employing 2.0 equiv of LiHMDS (HMDS = hexamethyldisilazide) or MOT-Bu ($\text{M} = \text{Li, Na, K}$) in tetrahydrofuran (THF) and quenching with 2.0 equiv of Ts_2O in dichloromethane (DCM). Unfortunately, the reactions generated less than satisfactory conversions (<5–97%) and E/Z selectivities (23:77–82:18). It has been reported previously that a highly E -selective enol silylation of acyclic ketones mediated by LiHMDS/ R_3N in toluene was readily achieved in which ≥ 2.0 equiv of LiHMDS were required for maximal E/Z selectivity via an eight-membered transition state (eq 1).¹⁹



We thus focused on the enolization and tosylate formation of ketone **1a** using 2.0 equiv of LiHMDS²⁰ with a tertiary alkyl amine (5.0 equiv) in toluene and quenching with 2.0 equiv of Ts_2O in DCM. As shown in Table 1, despite reasonable conversions (87–97%), reactions with bulkier amines tend to form more side products, which lowers the yield (Table 1, entries 1–3). Also, the chelating diamine base N,N,N',N' -tetramethylethylenediamine (TMEDA) only affords a 44:56 ratio of the E/Z stereoisomers (Table 1, entry 4). With Me_2NEt being the most promising amine, the stoichiometry of Me_2NEt was then examined (Table 1, entries 5–9). Two equivalents of Me_2NEt were optimal, affording quantitative conversion and a 99:1 E/Z ratio. At <2.0 equiv of Me_2NEt the E/Z selectivity remained high,

Table 1. Optimization of LiHMDS-Mediated Enolization and Tosylation^a

entry	R_3N	equiv of R_3N	conv ^b (%)	yield ^c (%)	$2a/2a'$ ^b
1	Cy_2NEt	5	97	90	99:1
2	$i\text{-Pr}_2\text{NEt}$	5	87	33	96:4
3	Et_3N	5	97	71	98:2
4	TMEDA	5	97	74	44:56
5	Me_2NEt	5	100	96	99:1
6	Me_2NEt	3	100	95	99:1
7	Me_2NEt	2	100	96 (88) ^d	99:1
8	Me_2NEt	1	99	84	98:2
9	Me_2NEt	0	75	56	97:3

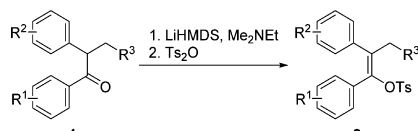
^aStandard conditions: ketone **1a** (1.0 mmol), LiHMDS in PhMe (0.90 M, 2.0 equiv, 2.2 mL), R_3N (0–5 equiv), PhMe (1.0 mL), 23 °C; then Ts_2O (2.0 equiv) in DCM (5.0 mL), 23 °C. ^bConversion and E/Z ratio were determined by HPLC analysis of the reaction mixture. ^cAssay yield of desired **2a** was determined by quantitative HPLC analysis. ^dThe number in parentheses is the isolated yield at both 1.0 mmol and 10.0 g (44.6 mmol) scale.

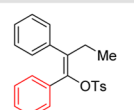
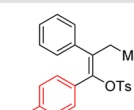
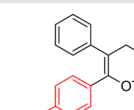
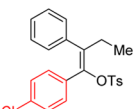
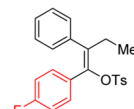
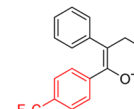
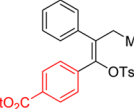
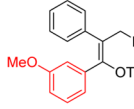
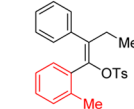
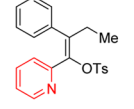
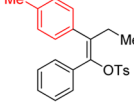
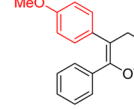
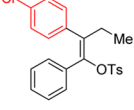
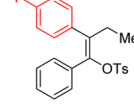
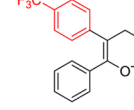
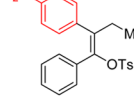
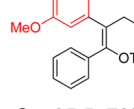
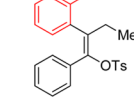
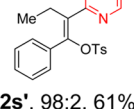
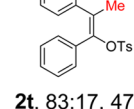
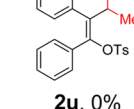
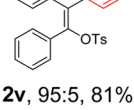
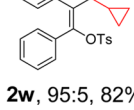
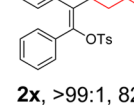
but the yield suffered (Table 1, entries 8, 9). A preparative-scale reaction using 10.0 g (44.6 mmol) of ketone **1a** under optimized conditions employing 2.0 equiv of LiHMDS and 2.0 equiv of Me_2NEt at 23 °C afforded pure E -isomer in 88% yield (Table 1, entry 7). The structure of E -isomer **2a** was determined by standard analytical methods including X-ray crystallography (Supporting Information).

We next investigated the scope and limitations of the enolization and tosylation reactions using the optimized conditions (Table 2). The aryl group directly connected to the carbonyl moiety tolerated electron-donating (4-Me, 4-MeO, 4-Cl) and electron-withdrawing (4-F, 4- CF_3 , 4- CO_2Et) substituents. All reactions afforded >95:5 E/Z selectivities and 66–87% isolated yields of the E -tosylate product (**2b–g**). Substitution of a 3-MeO group did not significantly impact the E/Z selectivity and yield (**2h**, 98:2, 87%). However, a 2-Me group substantially eroded the E/Z selectivity to 82:18, affording E -isomer **2i** and Z -isomer **2i'** in 61% and 12% yield, respectively, after chromatographic purification. The 2-pyridyl-substituted ketone afforded 98:2 E/Z selectivity and 82% isolated yield of the desired tosylate **2j**.

The aryl group distal to the carbonyl also tolerated electronically diverse substituents and afforded the tosylates **2k–q** in 95:5–99:1 E/Z selectivity and 75–95% isolated yields. Interestingly, the 2-Me substituent had a less profound effect on the E/Z selectivity (**2r**, 95:5) than in the case of **2i**, albeit with a lower isolated yield (50%). Surprisingly, the 2-pyridyl-substituted ketone generated a 2:98 E/Z selectivity favoring the unexpected Z -isomer **2s'** in 61% isolated yield. We attribute this reversal in selectivity to lithium chelation by the 2-pyridyl nitrogen forcing Z -enolate formation (eq 2).

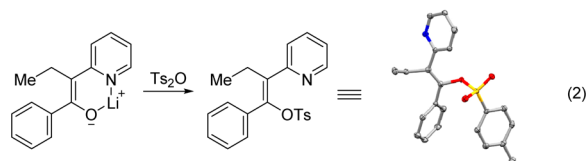
The enol tosylation reaction is sensitive to steric changes on the alkyl moiety proximal to the enolization site. Replacing the ethyl group with a smaller methyl group surprisingly afforded lower conversion and E/Z selectivity (83:17). After purification, only 47% of the E -tosylate **2t** was isolated, along with 10% of the Z -tosylate **2t'**. The hindered isopropyl moiety in **1u** afforded no

Table 2. Reaction Scope of Enol Tosylation^{a,b,c}


Tosylate products		
 2a , 99:1, 88% ^d	 2b , 98:2, 82%	 2c , 98:2, 66%
 2d , 98:2, 74%	 2e , >99:1, 78%	 2f , 96:4, 80%
 2g , 98:2, 87%	 2h , 98:2, 87%	 2i , 82:18, 61% ^e
 2j , 98:2, 82%	 2k , 95:5, 84%	 2l , 95:5, 75%
 2m , 98:2, 80%	 2n , 98:2, 76%	 2o , 98:2, 88%
 2p , 99:1, 95%	 2q , 95:5, 78%	 2r , 95:5, 50%
 2s' , 98:2, 61%	 2t , 83:17, 47% ^f	 2u , 0%
 2v , 95:5, 81%	 2w , 95:5, 82%	 2x , >99:1, 82%

^aStandard conditions: ketone **1** (2.0 mmol), LiHMDS in PhMe (0.90 M, 2.0 equiv, 4.4 mL), Me₂NEt (0.43 mL, 2.0 equiv), PhMe (2.0 mL), 23 °C; then Ts₂O (2.0 equiv) in DCM (10.0 mL), 23 °C. ^bE/Z ratio was determined by HPLC analysis of the reaction mixture. ^cIsolated yield. ^dThe reaction was also performed employing 10.0 g (44.6 mmol) of ketone **1a**. ^e12% of the Z-isomer **2i'** was isolated. ^f10% of the Z-isomer **2t'** was isolated.

product. Fortunately, the allyl-, cyclopropylmethyl-, and *n*-butyl-substituted ketones readily afforded the desired tosylates in high



yields and selectivities (**2v–x**). X-ray crystallographic analysis of tosylates **2** unambiguously established the *E*-olefin configuration (Supporting Information). A few representative X-ray structures are shown in Figure 2.

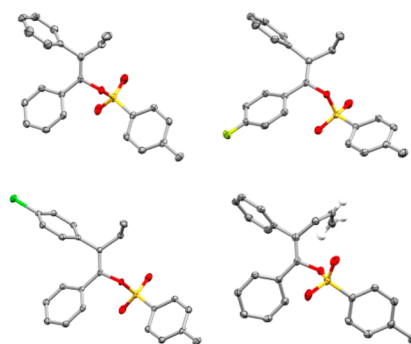


Figure 2. X-ray structures of *E*-tosylates **2a** and **2e** (top) and **2m** and **2v** (bottom).

Next, we examined the Suzuki–Miyaura coupling²¹ of *E*-tosylate **2a** and 4-fluorophenyl pinacol boronic ester (**3a**) by high-throughput screening of phosphine ligands using Pd(OAc)₂ as the precatalyst and K₃PO₄·H₂O as the base in PhMe/H₂O (3:1) at 70 °C. CMPhos,²² Xantphos,²³ and RuPhos²⁴ generated the highest conversions and lowest *E* → *Z* olefin isomerization (Figure 3).²⁵ Further validation and optimization led to the

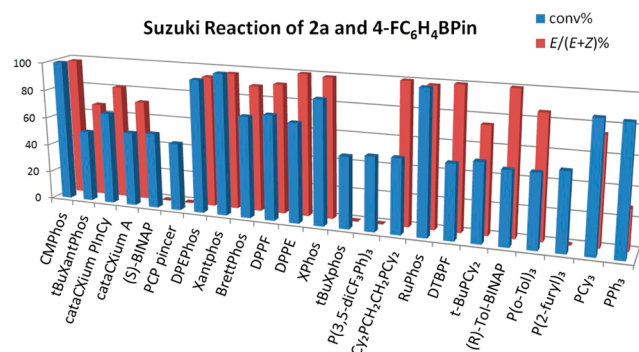
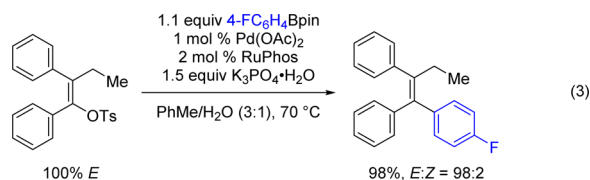


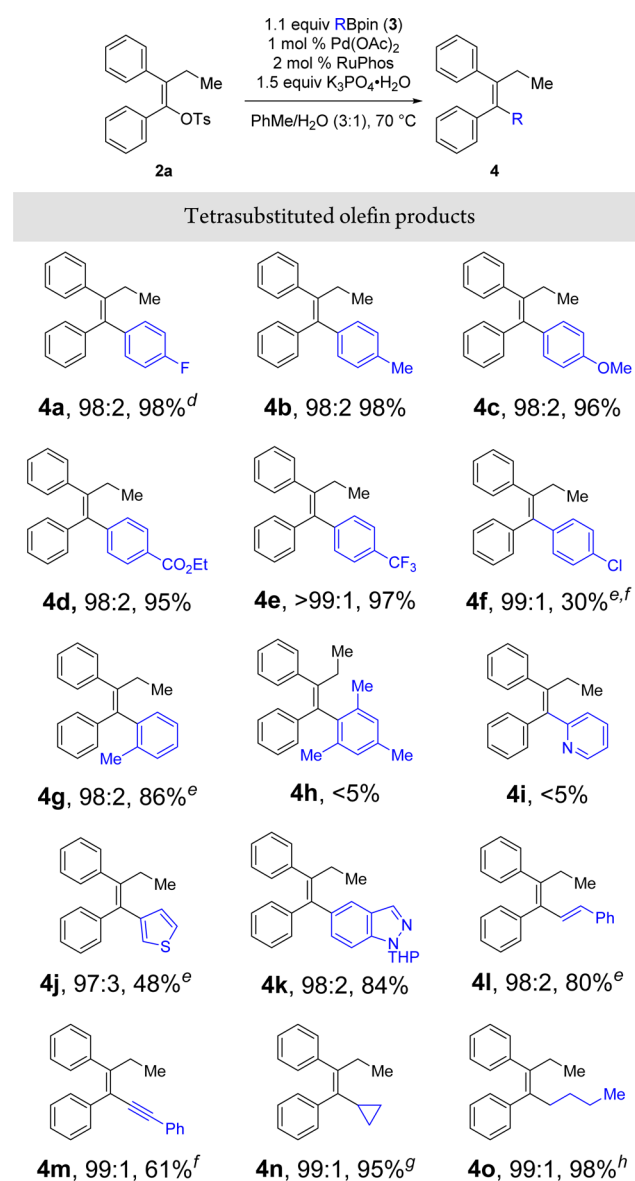
Figure 3. High-throughput screening of Suzuki–Miyaura coupling of *E*-tosylate **2a** and 4-FC₆H₄Bpin (**3a**).

optimal conditions using 1.0 equiv of *E*-tosylate **2a**, 1.1 equiv of boronic ester **3a**, 1 mol % of Pd(OAc)₂, 2 mol % of RuPhos, and 1.5 equiv of K₃PO₄·H₂O in PhMe/H₂O (0.5 M, 3:1) at 70 °C (eq 3). Under this set of conditions, the reaction afforded complete



conversion with only 2% of isomeric *Z*-olefin observed in the crude product. The *E*- and *Z*-isomers were inseparable by silica gel flash column chromatography. Thus, the desired tetrasubstituted olefin **4a** containing 2% of the *Z*-stereoisomer was isolated in 98% yield on a 5.0 g (12.7 mmol) scale (Table 3, entry 1). 4-Fluorophenylboronic acid and potassium 4-fluorophenyltrifluoroborate could be used in place of boronic ester **3a**, affording the same 98% yield and 98:2 *E/Z* ratio.

Table 3. Scope of Boronic Esters in the Suzuki–Miyaura Reaction^{a,b,c}



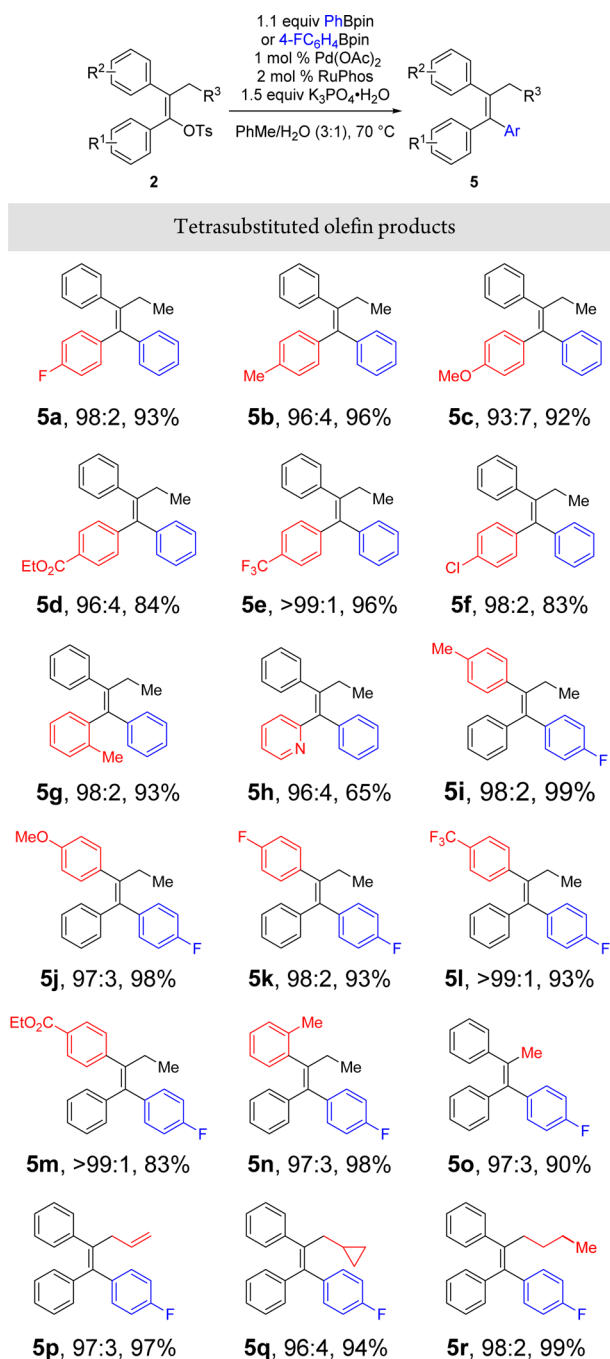
^aStandard conditions: *E*-tosylate **2a** (1.0 mmol), boronic ester (1.1 equiv), Pd(OAc)₂ (1 mol %), RuPhos (2 mol %), K₃PO₄·H₂O (1.5 equiv), PhMe/H₂O (1.5/0.5 mL), 70 °C. ^b*E/Z* ratios were determined by HPLC analysis of the isolated inseparable products. ^cIsolated yield. ^dThe reaction was also performed employing 5.0 g (12.7 mmol) of *E*-tosylate **2a**. ^ePd(OAc)₂ (2 mol %) and RuPhos (4 mol %) were employed. ^f2.1 equiv of boronic ester was employed. ^gNegishi conditions: *E*-tosylate **2a** (1.0 mmol), cyclopropylzinc bromide (1.1 equiv, 0.50 M in THF, 2 mL), LiCl (0.50 M in THF, 2.2 mL), Pd(OAc)₂ (1 mol %), RuPhos (2 mol %), 60 °C. ^h1.1 equiv of *n*-butylboronic acid was used.

E-Tosylate **2a** was coupled to a variety of electronically and sterically diverse boronic esters (**3**) under the optimized reaction conditions (Table 3). Phenylboronic esters substituted at the 4-position with either an electron-donating group (Me, MeO) or electron-withdrawing group (CO₂Et, CF₃) generated the cross-coupling products (**4b–e**) in excellent yields and *E/Z* selectivities. Reaction of 4-chlorophenyl pinacol boronic ester with *E*-tosylate **2a** afforded **4f** in 99:1 *E/Z* ratio but in a disappointing 30% yield (46% conversion) of the isolated product. We suspect that 4-chlorophenyl pinacol boronic ester oligomerizes under our standard reaction conditions. The sterically demanding 2-tolyl pinacol boronic ester required 2 mol % of Pd(OAc)₂ and 4 mol % of RuPhos to reach full conversion but still afforded 86% yield and 98:2 *E/Z* ratio of product **4g**. Highly hindered mesityl-derived pinacol boronic ester provided essentially no product **4h**. Similarly, 2-pyridyl pinacol boronic ester did not afford much of the coupling product **4i**, presumably due to the propensity of protodeboronation of the boronic ester under the reaction conditions.²⁶ By contrast, 3-thienyl and 5-indazolyl pinacol boronic esters coupled to give **4j–k** in moderate to good yields and excellent isomeric ratios. Vinyl, alkynyl, cyclopropyl, and alkyl boronic esters were also examined. As expected, styryl pinacol boronic ester produced an 80% yield and 98:2 ratio of the coupling product **4l**. The reaction with phenylethynyl pinacol boronic ester, however, required 2.1 equiv to reach completion, affording a 61% yield and 99:1 selectivity of **4m**. Cyclopropyl pinacol boronic ester failed to generate the desired olefin product possibly due to decomposition during the reaction. Gratifyingly, when *E*-tosylate **2a** was treated with cyclopropylzinc bromide under Negishi coupling²⁷ conditions, the reaction produced a 95% yield and 99:1 selectivity of olefin **4n**. Although *n*-butyl pinacol boronic ester did not afford a significant yield (<20%) of the coupling product, *n*-butylboronic acid underwent the Suzuki–Miyaura coupling smoothly, affording a 98% yield and 99:1 selectivity of olefin **4o**.

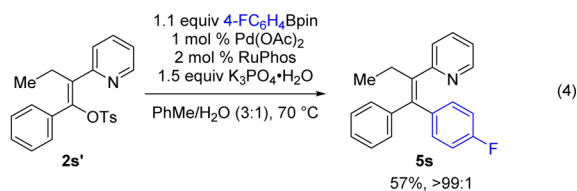
We examined the reactivity of a variety of *E*-tosylates (**2**) with phenyl pinacol boronic ester as a coupling partner (Table 4). The aryl group proximal to the tosylate can tolerate both electron-donating (Me, MeO, Cl) and electron-withdrawing (F, CO₂Et, CF₃) substituents at the 4-position as well as some steric congestion at the 2-position (**5a–g**), affording excellent yields and stereochemical integrity of the desired olefin products. *E*-Tosylate with a 2-pyridyl moiety afforded **5h** in 65% yield and 96:4 selectivity. Olefins **5a–g** are the complementary stereoisomers to olefins **4a–g** in Table 3. It is noteworthy that the modular nature of this methodology provides both isomers with excellent stereocontrol. Similarly, couplings with 4-fluorophenyl pinacol boronic ester showed that the aryl moiety distal to the tosylate also tolerates electron-donating and electron-withdrawing substituents at the 4-position (**5i–m**) as well as steric congestion at the 2-position (**5n**). Replacing the ethyl group with methyl, allyl, cyclopropylmethyl, or *n*-butyl moieties (**5o–r**) caused no erosion in yields or selectivities.

The pyridyl-containing *Z*-tosylate **2s'** unexpectedly generated in the enol tosylate reaction underwent the Suzuki–Miyaura reaction with 4-fluorophenyl pinacol boronic ester, forming the tetrasubstituted olefin **5s** in a moderate 57% yield with <1% olefin isomerization (eq 4).

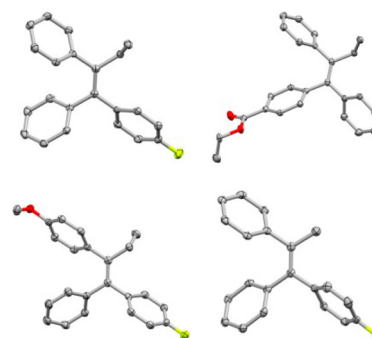
X-ray crystal structures of several tetrasubstituted olefins unambiguously established the geometry of the double bonds. Representative X-ray structures are shown in Figure 4.

Table 4. Scope of *E*-Tosylates in the Suzuki–Miyaura Reaction^{a,b,c}

^aStandard conditions: *E*-tosylate **2a** (1.0 mmol), boronic ester (1.1 equiv), Pd(OAc)₂ (1 mol %), RuPhos (2 mol %), K₃PO₄·H₂O (1.5 equiv), PhMe/H₂O (1.5/0.5 mL), 70 °C. ^b*E*/*Z* ratios were determined by HPLC analysis of the isolated inseparable products. ^cIsolated yield.



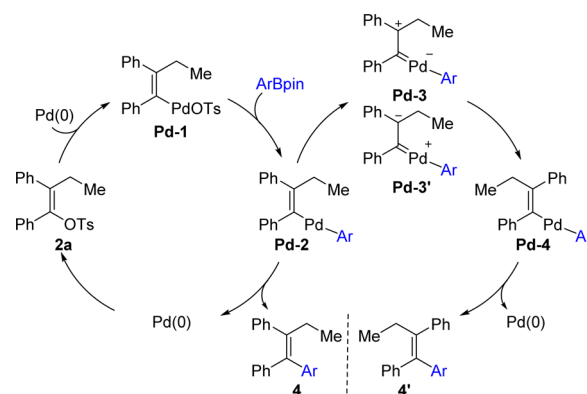
Olefin isomerizations have been previously noted in Suzuki–Miyaura couplings, but little is known about the cause of this

Figure 4. X-ray structures of olefins **4a** and **5d** (top) and **5j** and **5o** (bottom).

side-reaction.²⁵ We investigated the isomerization mechanism by examining the cross-coupling reaction of *E*-tosylate **2a** and 4-fluorophenyl pinacol boronic ester (**3a**). Subjecting product **4a** (*E*/*Z* = 98:2) to the standard coupling conditions caused no change in the *E*/*Z* ratio after 20 h, which indicates that the olefin product does not isomerize under the reaction conditions. Exclusion of light or addition of 2,6-di-*tert*-butyl-4-methylphenol (5 mol %) to the coupling reaction had no impact on the *E*/*Z* selectivity, arguing against a free radical mechanism. Treating either *E*-tosylate **2a** or its *Z*-isomer **2a'** with Pd(OAc)₂ omitting either RuPhos or the boronic ester or both showed no isomerization. Thus, we deem that a Pd(II)-catalyzed isomerization is an unlikely mechanism. Treating *E*-tosylate **2a** or its *Z*-isomer **2a'** with a low concentration (10 mol %) of boronic ester **3a** using either Pd(0) generated from Pd(OAc)₂ and RuPhos or RuPhos–Pd–G₃²⁸ showed that the tosylates do not isomerize.²⁹

On the basis of the above observations, we propose a plausible mechanism for olefin isomerization shown in Scheme 3. Similar

Scheme 3. Proposed Mechanism of Olefin Isomerization during Suzuki–Miyaura Coupling



to a mechanistic proposal published by Lipshutz,³⁰ the *E*-tosylate **2a** undergoes a stereospecific Pd(0) insertion to give Pd(II) intermediate **Pd-1**, which transmetalates with the aryl boronic ester to form intermediate **Pd-2**. A subsequent tautomerization of **Pd-2** to zwitterionic palladium carbenoid species³¹ **Pd-3** or **Pd-3'** erodes the stereointegrity to generate intermediate **Pd-4**. Intermediates **Pd-2** and **Pd-4** reductively eliminate to regenerate Pd(0) and produce the desired olefin **4** and its stereoisomer **4'**, respectively.

CONCLUSION

We have developed a highly stereoselective synthesis of tetrasubstituted acyclic all-carbon olefins via a stereoselective enolization and tosylate formation, followed by a palladium-catalyzed Suzuki–Miyaura cross-coupling with pinacol boronic esters in the presence of a Pd(OAc)₂/RuPhos catalytic system. Both the enol tosylation and Suzuki–Miyaura coupling reactions tolerate an array of electronically and sterically diverse substituents. Judicious choice of substrate and coupling partner provides access to either the *E*- or *Z*-olefin with excellent yield and stereochemical fidelity. Mechanistic probes show that erosion of stereointegrity occurs subsequent to transmetalation through a zwitterionic palladium carbenoid species. Isomerization was minimal in most cases under optimized cross-coupling conditions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05071.

Experimental details, spectral data, and ¹H and ¹³C NMR spectra (PDF)

Single-crystal X-ray data (PDF)

Crystallographic data in CIF format (ZIP)

AUTHOR INFORMATION

Corresponding Authors

*zhang.haiming@gene.com

*gosselin.francis@gene.com

ORCID

Chong Han: 0000-0002-2863-3921

David B. Collum: 0000-0001-6065-1655

Haiming Zhang: 0000-0002-2139-2598

Francis Gosselin: 0000-0001-9812-4180

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

In memory of Dr. Andrew McClory, who passed away on February 19, 2017. The authors would like to acknowledge Colin Masui (Genentech, Inc.) for his support on high-throughput screening, Dr. Sarah Robinson (Genentech, Inc.) for her assistance in collecting HRMS data, Dr. Antonio DiPasquale (Genentech, Inc.) for obtaining X-ray structures, and Professor Scott Denmark (University of Illinois at Urbana–Champaign) and Professor Stephen Buchwald (Massachusetts Institute of Technology) for helpful discussions. D.B.C. and K.A.M. thank the National Institutes of Health (GM077167 and GM039764) for financial support.

REFERENCES

(1) (a) Chiappe, C.; Detert, H.; Lenoir, D.; Pomelli, C. S.; Ruasse, M. *J. Am. Chem. Soc.* **2003**, *125*, 2864. (b) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Top. Curr. Chem.* **2000**, *207*, 89. (c) Columbus, L.; Biali, S. E. *J. Org. Chem.* **1994**, *59*, 3402. (d) Khoury, R. G.; Jaquinod, L.; Smith, K. M. *Chem. Commun.* **1997**, 1057. (e) Lykakis, I. N.; Vougioukalakis, G. C.; Orfanopoulos, M. *J. Org. Chem.* **2006**, *71*, 8740. (f) Stratakis, M.; Nencka, R.; Rabalakos, C.; Adam, W.; Krebs, O. *J. Org. Chem.* **2002**, *67*, 8758. (g) Treitel, N.; Eshdat, L.; Sheradsky, T.; Donovan, P. M.; Tykewski, R. R.; Scott, L. T.; Hopf, H.; Rabinovitz, M. *J. Am. Chem. Soc.* **2006**, *128*, 4703.

(2) (a) Schreivogel, A.; Maurer, J.; Winter, R.; Baro, A.; Laschat, S. *Eur. J. Org. Chem.* **2006**, *2006*, 3395. (b) Schultz, A.; Laschat, S.; Diele, S.; Nimtz, M. *Eur. J. Org. Chem.* **2003**, *2003*, 2829. (c) Schultz, A.; Diele, S.; Laschat, S.; Nimtz, M. *Adv. Funct. Mater.* **2001**, *11*, 441. (3) (a) DeGregorio, M. W.; Wiebe, V. J. *Tamoxifen and Breast Cancer*, 2nd ed.; Yale University Press: New Haven, CT, 1999. (b) Levenson, A. S.; Jordan, V. C. *Eur. J. Cancer* **1999**, *35*, 197410.1016/S0959-8049(99)00183-5. (4) McCague, R.; Leclercq, G.; Legros, N.; Goodman, J.; Blackburn, G. M.; Jarman, M.; Foster, A. B. *J. Med. Chem.* **1989**, *32*, 2527. (5) Connor, C. E.; Norris, J. D.; Broadwater, G.; Willson, T. M.; Gottardis, M. M.; Dewhirst, M. W.; McDonnell, D. P. *Cancer Res.* **2001**, *61*, 2917. (6) Lai, A.; Kahraman, M.; Govek, S.; Nagasawa, J.; Bonnefous, C.; Julien, J.; Douglas, K.; Sensintaffar, J.; Lu, N.; Lee, K.-j.; Aparicio, A.; Kaufman, J.; Qian, J.; Shao, G.; Prudente, R.; Moon, M. J.; Joseph, J. D.; Darimont, B.; Brigham, D.; Grillot, K.; Heyman, R.; Rix, P. J.; Hager, J. H.; Smith, N. D. *J. Med. Chem.* **2015**, *58*, 4888. (7) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (8) (a) Zhu, Y.; Wang, Z.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *114*, 8199. (b) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958. (c) Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603. (d) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Elsevier, 1991; Vol 7, p 389. (9) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P. G. *Chem. Rev.* **2014**, *114*, 2130. (10) (a) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698. (b) Shindo, M.; Matsumoto, K. *Top. Curr. Chem.* **2012**, *327*, 1. (11) (a) Simard-Mercier, J.; Flynn, A. B.; Ogilvie, W. W. *Tetrahedron* **2008**, *64*, 5472. (b) Yoshikawa, T.; Mori, S.; Shindo, M. *J. Am. Chem. Soc.* **2009**, *131*, 2092. (c) Zhang, X.; Larock, R. C. *Tetrahedron* **2010**, *66*, 4265. (d) Sakai, N.; Komatsu, R.; Uchida, N.; Ikeda, R.; Konakahara, T. *Org. Lett.* **2010**, *12*, 1300. (e) Lee, H. S.; Kim, K. H.; Kim, S. H.; Kim, J. N. *Adv. Synth. Catal.* **2012**, *354*, 2419. (f) Wen, Y.; Huang, L.; Jiang, H. J. *Org. Chem.* **2012**, *77*, 5418. (g) He, Z.; Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3699. (h) You, W.; Li, Y.; Brown, M. K. *Org. Lett.* **2013**, *15*, 1610. (i) Xue, F.; Zhao, J.; Hor, T. S. A.; Hayashi, T. *J. Am. Chem. Soc.* **2015**, *137*, 3189. (j) Gigant, N.; Quintin, F.; Bäckvall, J.-E. *J. Org. Chem.* **2015**, *80*, 2796. (k) Zhu, C.; Xu, G.; Ding, D.; Qiu, L.; Sun, J. *Org. Lett.* **2015**, *17*, 4244. (l) Ashida, Y.; Sato, Y.; Suzuki, T.; Ueno, K.; Kai, K.-i.; Nakatsujii, H.; Tanabe, Y. *Chem. - Eur. J.* **2015**, *21*, 5934. (m) Dai, J.; Wang, M.; Chai, G.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2016**, *138*, 2532. (n) La Cascia, E.; Cuenca, A. B.; Fernández, E. *Chem. - Eur. J.* **2016**, *22*, 18737. (12) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (13) Kelly, S. E. *Comp. Org. Syn* **1991**, *1*, 729. (14) Ager, D. J. In *Organic Reactions*; Wiley, 1990; Vol. 38; p 1. (15) *Modern Carbonyl Olefination*, Takeda, T., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (16) (a) McCague, R.; Leung, O.-T.; Jarman, M.; Kuroda, R.; Neidle, S.; Webster, G. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1201. (b) Ace, K. W.; Armitage, M. A.; Bellingham, R. K.; Blackler, P. D.; Ennis, D. S.; Hussain, N.; Lathbury, D. C.; Morgan, D. O.; O'Connor, N.; Oakes, G. H.; Passey, S. C.; Powling, L. C. *Org. Process Res. Dev.* **2001**, *5*, 479. (c) Valliant, J. F.; Schaffer, P.; Stephenson, K. A.; Britten, J. F. *J. Org. Chem.* **2002**, *67*, 383. (17) Doyle, M. P. In *Comprehensive Organometallic Chemistry*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, p 387. (18) (a) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332. (b) Barczak, N. T.; Rooke, D. A.; Menard, Z. A.; Ferreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7579. (c) Lawson, J. R.; Clark, E. R.; Cade, I. A.; Solomon, S. A.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7518. (d) Wang, X.; Studer, A. *J. Am. Chem. Soc.* **2016**, *138*, 2977. (19) Godenschwager, P. F.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, *130*, 8726.

(20) For the titration of LiHMDS, see: Lipton, M. P.; Sorensen, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.

(21) For reviews on Suzuki–Miyaura coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(22) Wong, S. M.; Yuen, O. Y.; Choy, P. Y.; So, C. M.; Kwong, F. Y. *Org. Synth.* **2016**, *93*, 14.

(23) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081.

(24) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2012**, *2*, 27.

(25) For previous reports on olefin isomerization during cross-coupling, see: (a) Christensen, M.; Nolting, A.; Shevlin, M.; Weisel, M.; Maligres, P. E.; Lee, J.; Orr, R. K.; Plummer, C. W.; Tudge, M. T.; Campeau, L.-C.; Ruck, R. T. *J. Org. Chem.* **2016**, *81*, 824. (b) Molinaro, C.; Scott, J. P.; Shevlin, M.; Wise, C.; Ménard, A.; Gibb, A.; Junker, E. M.; Lieberman, D. *J. Am. Chem. Soc.* **2015**, *137*, 999. (c) Lu, G.; Voigtritter, K. R.; Cai, C.; Lipshutz, B. H. *J. Org. Chem.* **2012**, *77*, 3700. (d) McKinley, N. F.; O'Shea, D. F. *J. Org. Chem.* **2006**, *71*, 9552.

(26) (a) Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, H. C. *Org. Lett.* **2009**, *11*, 381. (b) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345. (c) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302. (d) Ishiyama, T.; Isahida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813.

(27) For reviews on Negishi coupling, see: (a) Negishi, E.-i.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; p 815. (b) Negishi, E.-i. *Angew. Chem., Int. Ed.* **2011**, *50*, 6738.

(28) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916.

(29) The reactions reached 10% conversion and generated a 98:2 isomeric ratio favoring the desired olefin product.

(30) Krasovskiy, A.; Lipshutz, B. H. *Org. Lett.* **2011**, *13*, 3818.

(31) For reports proposing zwitterionic Pd carbene species, see: (a) Zargarian, D.; Alper, H. *Organometallics* **1991**, *10*, 2914. (b) Zargarian, D.; Alper, H. *Organometallics* **1993**, *12*, 712. (c) Brady, K. A.; Nile, T. A. *J. Organomet. Chem.* **1981**, *206*, 299. (d) de Vaal, P.; Dedieu, A. *J. Organomet. Chem.* **1994**, *478*, 121. (e) Amatore, C.; Bensalem, S.; Ghalem, S.; Jutand, A. *J. Organomet. Chem.* **2004**, *689*, 4642.