JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Regioselective and Stereospecific Rhodium-Catalyzed Allylic Cyanomethylation with an Acetonitrile Equivalent: Construction of Acyclic #-Quaternary Stereogenic Nitriles

Mai-Jan Tom, and P. Andrew Evans

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c02316 • Publication Date (Web): 02 Jun 2020

Regioselective and Stereospecific Rhodium-Catalyzed Allylic Cyanomethylation with an Acetonitrile Equivalent: Construction of Acyclic β-Quaternary Stereogenic Nitriles

Mai-Jan Tom[a] and P. Andrew Evans*[,a,b]

[a] Department of Chemistry, Queen's University, 90 Bader Lane, Kingston ON, K7L 3N6, Canada

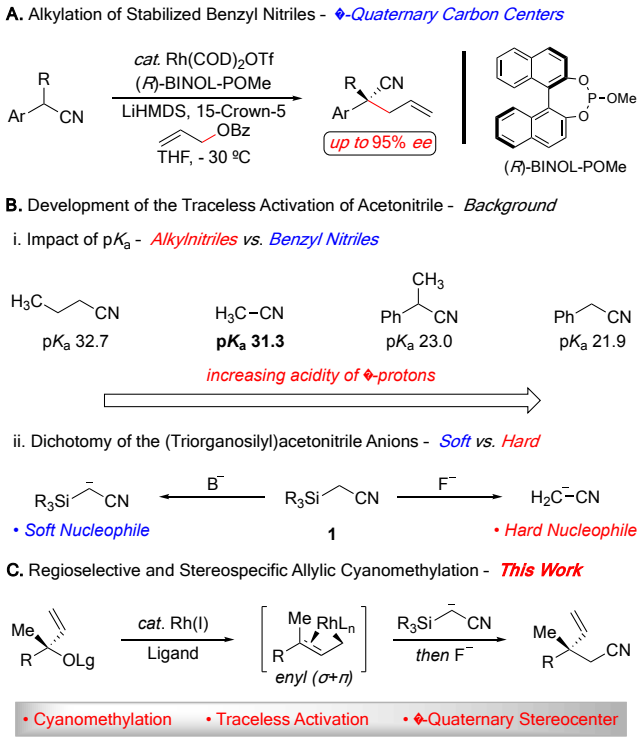
[b] Xiangya School of Pharmaceutical Sciences, Central South University, Changsha 410013, Hunan, P. R. of China

Supporting Information

ABSTRACT: A highly regioselective and stereospecific rhodium-catalyzed cyanomethylation of tertiary allylic carbonates for the construction of acyclic β-quaternary stereogenic nitriles is described. This protocol represents the first example of a metal-catalyzed allylic substitution reaction using a triorganosilyl-stabilized acetonitrile anion, which permits access to several carbonyl derivatives that are challenging to prepare using conventional pronucleophiles. The synthetic utility of the stereospecific cyanomethylation is further exemplified through the construction of the intermediate utilized in the total synthesis of both (+)-epilaurene and (+)–α-cuparenone.

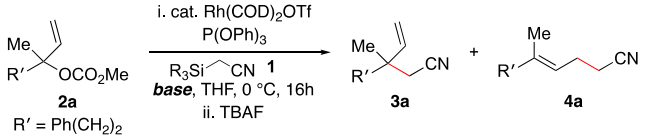
Alkyl nitriles represent versatile motifs that are omnipresent in an array of important bioactive natural products and pharmaceuticals, in addition to being versatile synthetic intermediates.[1,2] Consequently, the ability to readily employ alkyl nitriles as pronucleophiles in asymmetric transition-metal catalysis is highly desirable, albeit challenging because of the fluxional nature of the anion (*C*- *vs*. *N*-metalated).[3,4] For instance, the Lewis basic nature of nitrile anions can render the transition-metal unreactive by binding the nitrogen and carbon atoms, in addition to forming stable dinuclear complexes.[4,5] Furthermore, the alkylation of primary nitriles often results in *bis*-alkylation products, because of the similar acidity of the α-protons in the substrate and product. Nevertheless, we recently reported the first enantioselective rhodium-catalyzed allylic alkylation of α-substituted benzyl nitriles for the construction of challenging acyclic α-quaternary nitrile stereocenters (Scheme 1A).[6] We envisaged the ability to employ a simple alkyl nitrile, such as acetonitrile, would provide a complementary approach, given that it would access the corresponding acyclic β-quaternary stereogenic nitriles.[7,8] Nevertheless, the direct transition metal-catalyzed cyanomethylation reaction has been underdeveloped,[9] which can presumably be ascribed to the aforementioned challenges and the fact that it constitutes a hard unstabilized carbanion (Scheme 1B, i).[10,11] As a result, several synthetic equivalents has been developed that circumvent the limitations of the acetonitrile anion and thereby facilitate selective cyanomethylations,[12,13] in which the (trimethylsilyl)acetonitrile (TMSAN) has emerged as a particularly versatile synthon for conventional electrophiles.[14] A key and striking feature with this pronucleophile is the ability to generate either the silyl stabilized anion or the unstabilized carbanion *via* the direct deprotonation or cleavage of the carbon-silicon bond, respectively (Scheme 1B, ii).[16-17a] Notably, the trimethylsilyl stabilized acetonitrile carbanion undergoes conjugate addition in the absence of copper, which further supports the soft nature of the nucleophile.[17] Surprisingly, the application of either of these anions in metal-catalyzed cross-coupling reactions has been

Scheme 1. Background for the Development of the Rhodium-Catalyzed Allylic Cyanomethylation



limited.[18,19] We envisioned using the *stabilized* acetonitrile carbanion in a rhodium-catalyzed allylic substitution with tertiary allylic carbonates would provide a novel quaternary allylic cyanomethylation product bearing two synthetic handles. Moreover, given the versatility of nitriles, this transformation would provide a unified strategy to access several related carbonyl derivatives that have proven challenging for conventional pronucleophiles.[20,21] Herein, we now describe the first highly regioselective and stereospecific rhodium-catalyzed cyanomethylation of tertiary allylic carbonates through the traceless activation of an acetonitrile carbanion for the construction of acyclic β-quaternary stereogenic nitriles (Scheme 1C).

Table 1. Optimization of the Regioselective and Stereospecific Rhodium-Catalyzed Allylic Cyanomethylation using Tertiary Carbonate 2a[a]

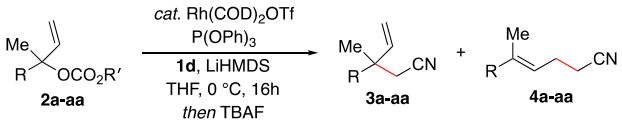


entry	base	1, R_3 =		3a:4a (b/l) [b]	Yield of 3a (%) [c]
1[d]	^{n}BuLi	Me_3	**a**	≥19:1	32
2[d]	^{s}BuLi	"	"	≥19:1	11
3[d]	LDA	"	"	≥19:1	30
4[d]	LiHMDS	"	"	≥19:1	35
5	"	Et_3	**b**	≥19:1	40
6	"	$^i Pr_3$	**c**	≥19:1	10
7	**LiHMDS**	**^{t}BuMe$_2$**	**d**	**≥19:1**	**90 (88)[e]**

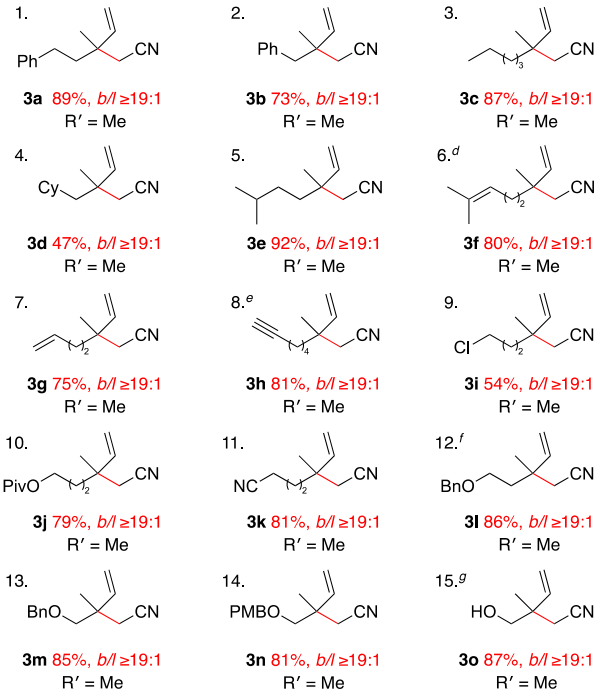
[a] All reactions were performed on a 0.25 mmol reaction scale using 10 mol % $Rh(COD)_2OTf$, 30 mol % $P(OPh)_3$, 2.0 equiv **1**, and 1.9 equiv of base in THF (2.5 mL) at 0 °C to room temperature for *ca.* 16 hours. [b] Regioselectivity was determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixtures. [c] GC yields of **3a**. [d] No TBAF. [e] Isolated yield of **3a**.

Table 1 outlines the optimization of the regioselective rhodium-catalyzed allylic cyanomethylation. In accordance with our hypothesis, we examined the traceless activation of an acetonitrile equivalent that provides a stabilized nucleophile to match the reactivity of the soft *enyl* organorhodium intermediate.[22] Treatment of tertiary allylic carbonate **2a** with the lithium anion of commercially available TMSAN (**1a**), in the presence of triphenyl phosphite *modified* $Rh(COD)_2OTf$, furnished the branched regioisomer **3a** in 32% yield with excellent regioselectivity (Table 1, entry 1). In light of the relatively poor efficiency, we elected to explore the impact of base on the reaction. To this end, a series of bases were examined, in which *sec*-butyllithium was significantly less efficient (entry 2), and the reactions with lithium diisopropylamine (LDA) and lithium bis(trimethylsilyl)amide (LiHMDS) provided comparable efficiency to that with *n*-butyllithium (entry

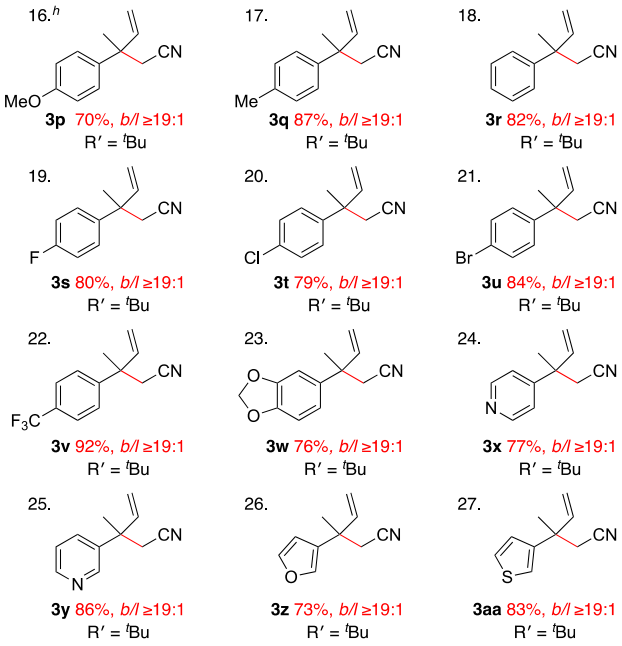
Table 2. Scope of the Regioselective Rhodium-Catalyzed Allylic Cyanomethylation Reaction[a,b,c]



Alkyl Carbonate Scope



Aryl Carbonate Scope



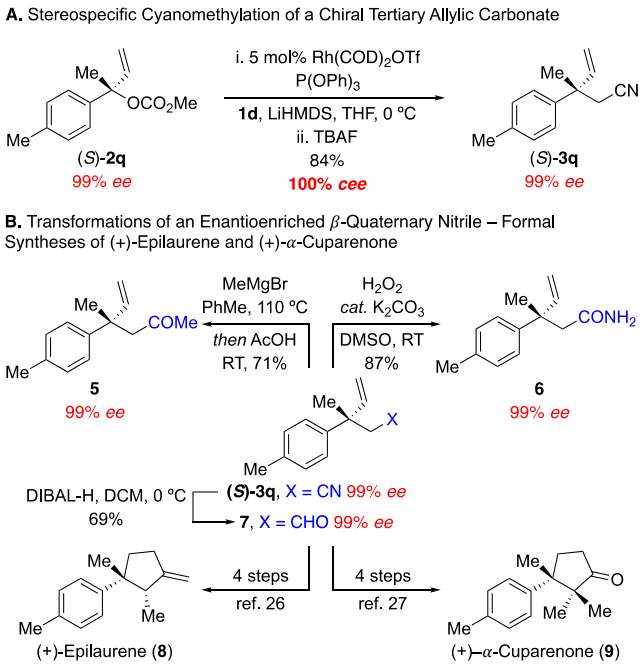
[a] All reactions were performed on a 0.5 mmol reaction scale using 10 mol % $Rh(COD)_2OTf$, 30 mol % $P(OPh)_3$, 2.0 equiv **1d** and 1.9 equiv of LiHMDS in THF (5.0 mL) at 0 °C to room temperature for *ca.* 16 hours. [b] Regioselectivity was determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixtures. [c] Isolated yields. [d] Employing (*R*)-**2f** (94% *ee*) provides (*S*)-**3f** (94% *ee*) in 100% *cee*. [e] From TMS-protected alkyne. [f] Isolated yield over two steps. [g] From TBS-protected alcohol. [h] One-pot protocol from the tertiary allylic alcohol.

1 *vs* entries 3 and 4). Interestingly, there is no evidence of polyalkylation at the α-position of the β-quaternary nitrile **3a**, which suggested that the stability of the pronucleophile was the reason for the reduced efficiency. Consequently, we envisioned that replacing the trimethylsilyl group, which is prone to desilylation by alkoxides generated from the leaving group,[16] with more sterically hindered silyl groups may improve the efficiency of this process. In accord with this reasoning, the bulkier silyl groups would be retained and thereby require the *in situ* addition of fluoride, albeit the isolation of the α-silyl nitriles may also be desired in some cases.[23] Interestingly, the (triethylsilyl)acetonitrile (**1b**) is slightly more efficient (entry 5), whereas the (triisopropylsilyl)acetonitrile (**1c**) is inferior (entry 6). Gratifyingly, the (*tert*-butylsilyl)acetonitrile (**1d**) provided the optimal pronucleophile for this process, which afforded the β-quaternary nitrile **3a** in 88% isolated yield in a highly regioselective manner.[24,25] *Hence, the silyl group plays a critical role in the generation, stability and reactivity of the α-cyano carbanion in this type of alkylation reaction.*

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 7) to a variety of acyclic tertiary carbonates **2a-aa**. The reaction is highly selective for carbonates containing an aromatic substituent at both the β- and γ-positions, albeit less efficient with β-substitution (Table 2, entries 1 and 2). Interestingly, the reaction also tolerates various tertiary carbonates containing alkyl substitution patterns, including linear alkyl chains (entry 3), in addition to β- and γ-branched alkyl carbonates to provide moderate to excellent yield (entries 4 and 5). More importantly, the reaction affords the corresponding β-quaternary nitriles for substrates with trisubstituted and terminal olefins (entries 6 and 7), in addition to providing terminal alkynes, derived from the TMS-protected internal alkyne, with excellent selectivity (entry 8). Notably, the reaction is chemoselective as exemplified by the primary alkyl chloride, ester and nitrile-containing tertiary carbonates, which are challenging for more conventional carbanions (entries 9-11). Moreover, the reaction can be performed in the presence of benzyl protected γ- and β-alcohol containing carbonates (entries 12-14), while also providing the free alcohol after *in situ* deprotection of the OTBS ether in good yield (entry 15). Furthermore, the scope of the tertiary allylic carbonates can be readily expanded to aryl and heteroaryl tertiary carbonates (entries 16-27). In this case, a range of electron-rich and electron-deficient aryl carbonates provide the corresponding β-quaternary nitriles in excellent yield and with high regioselectivity (entries 16-23). The reaction can also be conducted using a *one-pot* procedure from the tertiary allylic alcohol to furnish the desired product after *in situ* generation of the allylic carbonate (entry 16). Similarly, several tertiary heteroaromatic allylic carbonates provide excellent efficiency and selectivity in this process (entries 24-27), which are applicable to medicinal chemistry. Hence, a key and striking feature with this transformation is the high selectivity favoring the branched nitrile products in all cases, in which there was no detectable linear regioisomer (by 500 MHz ^{1}H NMR analysis of the crude reaction mixtures). Overall, this transformation provides a direct, efficient and selective route to access an array of β-quaternary substituted nitriles.

To further highlight the synthetic utility of this transformation, we elected to examine the stereospecific rhodium-catalyzed cyanomethylation using a chiral nonracemic tertiary carbonate.[26] Treatment of the enantiomerically enriched tertiary allylic carbonate (*S*)-**2q** under the optimal reaction conditions, using a *decreased catalyst loading*, furnished the chiral β-substituted nitrile (*S*)-**3q** in 84% yield in a highly regioselective and stereospecific manner (100% *cee*) (Scheme 2A).[27] Gratifyingly, the stereospecific nature of this transformation is demonstrated with an alkyl substituted allylic carbonate (*R*)-**2f**, which also proceeds with 100% *cee,* thus demonstrating that this is generally applicable to a range of substrates (*vide supra*).

Scheme 2. Synthetic Utility of the Rhodium-Catalyzed Allylic Cyanomethylation.



Scheme 2B illustrates the synthetic utility of the nitrile products through the conversion of (*S*)-**3q** into an array of important functional groups, which also permits the stereochemical course of the alkylation to be established. Specifically, the methyl ketone **5**, which is of known absolute configuration, was readily obtained through the addition of methylmagnesium bromide and subsequent hydrolysis of the imine.[28] Hence, the reaction proceeds through a double inversion process to provide overall retention of configuration, which confirms the anion of

(*tert*-butylsilyl)acetonitrile (**1d**) behaves as a soft nucleophile in this transformation. Furthermore, the level of stereospecificity is remarkable, given our previous efforts with cyanohydrin pronucleophiles.[29] The hydrolysis of the nitrile (*S*)-**3q** under basic reaction conditions with hydrogen peroxide affords the corresponding amide **6** in excellent yield and with retention of stereochemistry. Additionally, the reduction of the nitrile (*S*)-**3q** with DIBAL-H provides the aldehyde **7**, to further demonstrate the utility of the nitrile products. Notably, the preparation of the β-quaternary aldehyde **7** provides a key intermediate in the syntheses of the natural products (+)-laurene (**8**) and (+)-α-cuparenone (**9**).[30]

In conclusion, we have developed a highly regioselective and stereospecific rhodium-catalyzed allylic cyanomethylation of both aryl and alkyl chiral tertiary allylic carbonates with a novel acetonitrile synthetic equivalent. This transformation demonstrates the first regioselective alkylation of tertiary allylic carbonates with a triorganosilyl-stabilized nitrile anion and affords an efficient one-pot access to acyclic β-quaternary nitriles. Additionally, the synthetic utility of the nitrile products is exemplified in functional group transformations, one of which permits formal syntheses of (+)-epilaurene and (+)-α-cuparenone. Hence, given the utility of this transformation to prepare important β-quaternary nitriles, ketones, aldehydes and amides, we anticipate that it will provide a useful method for the construction of challenging natural products and pharmaceuticals.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures, spectral data and NMR spectra for all compounds. The Supporting Information is available free of charge on the ACS publication website at DOI:

AUTHOR INFORMATION

Corresponding Author.

*Andrew.Evans@chem.queensu.ca

ACKNOWLEDGMENT

We sincerely thank the National Sciences and Engineering Research Council (NSERC) for a *Discovery Grant* for financial support. NSERC is also thanked for supporting a *Tier 1 Canada Research Chair* (PAE). We also thank Queen's University for an *R. S. McLaughlin Fellowship* (MJT) and the Government of Ontario for an *Ontario Graduate Scholarship* (MJT).

REFERENCES

(1) For select reviews on nitrile-containing natural products and pharmaceuticals, see: (a) Fleming, F. F. Nitrile-Containing Natural Products. *Nat. Prod. Rep.* **1999**, *16*, 597. (b) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *J. Med. Chem.* **2010**, *53*, 7902.

(2) For a recent review on cyanoalkylations, see: López, R.; Palomo, C. Cyanoalkylation: Alkylnitriles in Catalytic C–C Bond-Forming Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 13170.

(3) Fleming, F. F.; Shook, B. C. Nitrile Anion Cyclizations. *Tetrahedron* **2002**, *58*, 1.

(4) For examples of nitriles coordinating to transition-metals, see: (a) Purzycki, M.; Liu, W.; Hilmersson, G.; Fleming, F. F. Metalated Nitriles: N- and C-coordination preferences of Li, Mg, and Cu Cations. *Chem. Commun.* **2013**, *49*, 4700. (b) Nelin, C. J.; Bagnus, P. S.; Philpott, M. R. The Nature of the Bonding of CN to Metals and Organic Molecules. *J. Chem. Phys.* **1987**, *87*, 2170.

(5) For examples of nitriles coordinating to rhodium, see: (a) Sawamura, M.; Sudoh, M.; Ito, Y. An Enantioselective Two-Component Catalyst System: Rh–Pd-Catalyzed Allylic Alkylation of Activated Nitriles. *J. Am. Chem. Soc.* **1996**, *118*, 3309. (b) Evans, P. A.; Kennedy, L. J. Regioselective Rhodium-Catalyzed Allylic Alkylation/Ring-Closing Metathesis Approach to Carbocycles. *Tetrahedron Lett.* **2001**, *42*, 7015.

(6) Turnbull, B. W. H.; Evans, P. A. Enantioselective Rhodium-Catalyzed Allylic Substitution with a Nitrile Anion: Construction of Acyclic Quaternary Carbon Stereogenic Centers. *J. Am. Chem. Soc.* **2015**, *137*, 6156.

(7) For a review on the construction of β-stereocenters using π-allyl chemistry, see: Oliver, S.; Evans, P. A. Transition-Metal-Catalyzed Allylic Substitution Reactions: Stereoselective Construction of α- and β-Substituted Carbonyl Compounds. *Synthesis* **2013**, *45*, 3179.

(8) For recent reviews for the construction of acyclic quaternary carbon stereogenic centers, see: (a) Das, J. P.; Marek, I. Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers in Acyclic Systems. *Chem. Commun.* **2011**, *47*, 4593. (b) Feng, J.; Holmes, M.; Krische, M. J. Acyclic Quaternary Carbon Stereocenters via Enantioselective Transition Metal Catalysis. *Chem. Rev.* **2017**, *117*, 12564.

(9) For select examples of transition metal-catalyzed cyanomethylations using acetonitrile, see: (a) Bunescu, A.; Wang, Q.; Zhu, J. Copper-Catalyzed Cyanomethylation of Allylic Alcohols with Concomitant 1,2-Aryl Migration: Efficient Synthesis of Functionalized Ketones Containing an α-Quaternary Center. *Angew. Chem., Int. Ed.* **2015**, *54*, 3132. (b) Liu, Y.; Yang, K.; Ge, H. Palladium-Catalyzed Ligand-Promoted Site-Selective Cyanomethylation of Unactivated $C(sp^3)$–H bonds with Acetonitrile. *Chem. Sci.* **2016**, *7*, 2804.

(10) (a) For the pK_a of butyronitrile, see: Judka, M.; Wojtasiewicz, A.; Danikiewicz, W.; Makosza, M. Halogens in γ-Position Enhance the Acidity of Alkyl Aryl Sulfones and Alkane Nitriles. *Tetrahedron* **2007**, *63*, 8902. (b) For the pK_a of acetonitrile, α-methylbenzyl cyanide and benzyl cyanide, see: Bordwell, F. G. Equilibrium Acidities in Dimethyl Sulfoxide Solution. *Acc. Chem. Res.* **1988**, *21*, 456.

(11) For a more detailed discussion on the mechanism for the rhodium-catalyzed allylic substitution with a hard and soft nucleophile, see: (a) Evans, P. A.; Leahy, D. K. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Ch. 10, pp 191-214. (b) Turnbull, B. W. H.; Evans, P. A. Asymmetric Rhodium-Catalyzed Allylic Substitution Reactions: Discovery, Development and Applications to Target-Directed Synthesis. *J. Org. Chem.* **2018**, *83*, 11463.

(12) For approaches using a decarboxylative strategy to provide the cyanomethyl moiety, see: (a) Hyodo, K.; Kondo, M.; Funahashi, Y.; Nakamura, S. Catalytic Enantioselective Decarboxylative Cyanoalkylation of Imines by Using Palladium Pincer Complexes with C_2-Symmetric Chiral Bis(imidazoline)s. *Chem. Eur. J.* **2013**, *19*, 4128. (b) Diosdado, S.; López, R.; Palomo, C. Ureidopeptide-Based Brønsted Bases: Design, Synthesis and Application to the Catalytic Enantioselective Synthesis of β-Amino Nitriles from (Arylsulfonyl)acetonitriles. *Chem. Eur. J.* **2014**, *20*, 6526. (c) Matsunami, A.; Takizawa, K.; Sugano, S.; Yano, Y.; Sato, H.; Takeuchi, R. Synthesis of Chiral Homoallylic Nitriles by Iridium-Catalyzed Allylation of Cyanoacetates. *J. Org. Chem.* **2018**, *83*, 12239.

(13) For an example of an alternative acetonitrile equivalent, see: Hock, K. J.; Knorrscheidt, A.; Hommelsheim, R.; Ho, J.; Weissenborn, M. J.; Koenigs, R. M. Tryptamine Synthesis by Iron Porphyrin Catalyzed C–H Functionalization of Indoles with Diazoacetonitrile. *Angew. Chem., Int. Ed.* **2019**, *58*, 3630.

(14) For select examples of the addition of TMSAN to aldehydes, ketones, imines and epoxides, see: (a) Matsuda, I.; Murata, S.; Ishii, Y.

A Simple Preparation of Trimethylsilylacetonitrile and a Novel Ring-Opening of Epoxides with Trimethylsilylacetonitrile Anion. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 26. (b) Kawano, Y.; Fujisawa, H.; Mukaiyama, T. Lewis Base-Catalyzed Cyanomethylation of Aldimines with Trimethylsilylacetonitrile. *Chem. Lett.* **2005**, *34*, 1134. (c) Kawano, Y.; Kaneko, N.; Mukaiyama, T. Lewis Base-Catalyzed Cyanomethylation of Carbonyl Compounds with (Trimethylsilyl)acetonitrile. *Chem. Lett.* **2005**, *34*, 1508.

(15) For an example of forming the lithiated TMSAN anion using ^{n}BuLi, followed by cleavage of the TMS, see: D'hooghe, M.; Vervisch, K.; De Kimpe, N. Synthesis of 1-Arylmethyl-2-(2-cyanoethyl)aziridines and their Rearrangement into Novel 2-(Aminomethyl)cyclopropanecarbonitriles. *J. Org. Chem.* **2007**, *72*, 7329.

(16) For an example of the formation of TMSAN anion *via* cleavage of the carbon-silicon bond using a fluoride source, see: Palomo, C.; Aizpurua, J. M.; López, M. C.; Lecea, B. Fluoride-ion Mediated Reaction Between Trimethylsilylacetonitrile and Carbonyl Compounds. A New Synthesis of β-Trimethylsilyloxy Nitriles. *J. Chem. Soc., Perkin Trans. I*, **1989**, 1692.

(17) For select examples of TMSAN undergoing a 1,4-addition in the absence of copper, see: (a) Tomioka, K.; Koga, K. Conjugate Addition Reaction of Trimethylsilylacetonitrile with α,β-Unsaturated Carbonyl Compounds. Synthetic Studies Toward Sesbanimide. *Tetrahedron Lett.* **1984**, *25*, 1599. (b) Paquette, L. A.; Friedrich, D.; Pinard, E.; Williams, J. P.; St. Laurent, D.; Roden, B. A. Total Synthesis of the Tetracyclic Diquinane Lycopodium Alkaloids Magellanine and Magellaninone. *J. Am. Chem. Soc.* **1993**, *115*, 4377. (c) Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. Synthesis of (+)-Complanadine A, an Inducer of Neurotrophic Factor Excretion. *J. Am. Chem. Soc.* **2010**, *132*, 5924.

(18) TMSAN has been used for an enantioselective copper-catalyzed cyanomethylation of acetophenone to furnish the corresponding β-hydroxy nitrile in 48% yield and 49% *ee*, see: Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147.

(19) The palladium-catalyzed α-arylation of TMSAN (**1a**) using zinc fluoride has been reported, see: Wu, L.; Hartwig, J. F. Mild Palladium-Catalyzed Selective Monoarylation of Nitriles. *J. Am. Chem. Soc.* **2005**, *127*, 15824.

(20) For select examples of the preparation of β-ternary ketones, see: (a) Evans, P. A.; Leahy, D. K. Regioselective and Enantiospecific Rhodium-Catalyzed Allylic Alkylation Reactions Using Copper(I) Enolates: Synthesis of (–)-Sugiresinol Dimethyl Ether. *J. Am. Chem. Soc.* **2003**, *125*, 8974. (b) Graening, T.; Hartwig, J. F. Iridium-Catalyzed Regio- and Enantioselective Allylation of Ketone Enolates. *J. Am. Chem. Soc.* **2005**, *127*, 17192. (c) Weix, D. J.; Hartwig, J. F. Regioselective and Enantioselective Iridium-Catalyzed Allylation of Enamines. *J. Am. Chem. Soc.* **2007**, *129*, 7720. (d) Chen, M.; Hartwig, J. F. Iridium-Catalyzed Enantioselective Allylic Substitution of Unstabilized Enolates Derived from α,β-Unsaturated Ketones. *Angew. Chem., Int. Ed.* **2014**, *53*, 8691. (e) Chen, M.; Hartwig, J. F. Iridium-Catalyzed Regio- and Enantioselective Allylic Substitution of Silyl Dienolates Derived from Dioxinones. *Angew. Chem., Int. Ed.* **2014**, *53*, 12172. (f) Chen, M.; Hartwig, J. F. Iridium-Catalyzed Enantioselective Allylic Substitution of Enol Silanes from Vinylogous Esters and Amides. *J. Am. Chem. Soc.* **2015**, *137*, 13972.

(21) For select examples for the preparation of β-ternary amides, esters and aldehydes, see: (a) Sempere, Y.; Carreira, E. M. Trimethyl Orthoacetate and Ethylene Glycol Mono-Vinyl Ether as Enolate Surrogates in Enantioselective Iridium-Catalyzed Allylation. *Angew. Chem., Int. Ed.* **2018**, *57*, 7654. (b) Sempere, Y.; Alfke, J. L.; Rössler, S. L.; Carreira, E. M. Morpholine Ketene Aminal as Amide Enolate Surrogate in Iridium-Catalyzed Asymmetric Allylic Alkylation. *Angew. Chem., Int. Ed.* **2019**, *58,* 9537.

(22) Evans, P. A.; Nelson, J. D. Conservation of Absolute Configuration in the Acyclic Rhodium-Catalyzed Allylic Alkylation Reaction: Evidence of an *Enyl* (σ + π) Organorhodium Intermediate. *J. Am. Chem. Soc.* **1998**, *120*, 5581.

(23) The crude α-silyl nitrile is obtained as a 1.5:1 mixture of diastereoisomers prior to it cleavage with TBAF.

(24) For the preparation and application of (*tert*-butylsilyl)acetonitrile (**1d**), see: Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. Regio- and Stereocontrolled Synthesis of Allenic and Acetylenic Derivatives. Organotitanium and Boron Reagents. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768.

(25) Attempts to utilize acetonitrile (2 equiv) with a variety of other bases and temperatures failed to provide any product.

(26) (a) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. Enantiodivergent Conversion of Chiral Secondary Alcohols into Tertiary Alcohols. *Nature* **2008**, *456*, 778. (b) Bagutski, V.; French, R. M.; Aggarwal, V. K. Full Chirality Transfer in the Conversion of Secondary Alcohols into Tertiary Boronic Esters and Alcohols using Lithiation-Borylation Reactions. *Angew. Chem., Int. Ed.* **2010**, *49*, 5142.

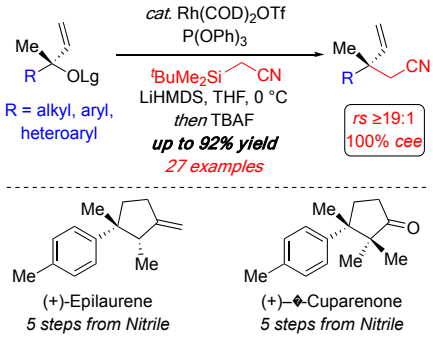
(27) The term conservation of enantiomeric excess (*cee*) = (*ee* of product ÷ *ee* of starting material) × 100. For details, please see: Evans, P. A.; Robinson, J. E.; Nelson, J. D. Enantiospecific Synthesis of Allylamines *via* the Regioselective Rhodium-Catalyzed Allylic Amination Reaction. *J. Am. Chem. Soc.* **1999**, *121*, 6761.

(28) Jung, B.; Hoveyda, A. H. Site- and Enantioselective Formation of Allene-Bearing Tertiary or Quaternary Carbon Stereogenic Centers through NHC–Cu-Catalyzed Allylic Substitution. *J. Am. Chem. Soc.* **2012**, *134*, 1490.

(29) For the stereospecific rhodium-catalyzed allylic substitution employing acyl anion equivalents, see: (a) Evans, P. A.; Oliver, S.; Chae, J. Rhodium-Catalyzed Allylic Substitution with an Acyl Anion Equivalent: Stereospecific Construction of Acyclic Quaternary Carbon Stereogenic Centers. *J. Am. Chem. Soc.* **2012**, *134*, 19314. (b) Evans, P. A.; Oliver, S. Regio- and Enantiospecific Rhodium-Catalyzed Allylic Substitution with an Acyl Anion Equivalent. *Org. Lett.* **2013**, *15*, 5626. (c) Turnbull, B. W. H.; Oliver, S.; Evans, P. A. Stereospecific Rhodium-Catalyzed Allylic Substitution with Alkenyl Cyanohydrin Pronucleophiles: Construction of Acyclic Quaternary Substituted α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **2015**, *137*, 15374.

(30) For the synthesis of (+)-epilaurene (**8**), see: (a) Fadel, A.; Canet, J.-L.; Salaün, J. Asymmetric Construction of Quaternary Carbons from Chiral Malonates: Total Syntheses of (+)-Epilaurene and (–)-Isolaurene. *Tetrahedron: Asymmetry* **1993**, *4*, 27. For the synthesis of (+)-α-cuparenone (**9**), see: (b) Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. Synthetic Approach to (–)-Cuparenone by Rhodium-Catalyzed Cyclization. *Chem. Pharm. Bull.* **1985**, *33*, 4821. (c) Kumar, R.; Halder, J.; Nanda, S. Asymmetric Total Synthesis of (*R*)-α-Cuparenone, (*S*)-Cuparene and Formal Synthesis of (*R*)-β-Cuparenone through Meinwald Rearrangement and Ring Closing Metathesis (RCM) Reaction. *Tetrahedron* **2017**, *73*, 809.

Regioselective and Stereospecific Rhodium-Catalyzed Allylic Cyanomethylation with an Acetonitrile Equivalent: Construction of Acyclic β-Quaternary Stereogenic Nitriles



Mai-Jan Tom and P. Andrew Evans*