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ARTICLE

A general Pd−catalyzed α− and γ−benzylation of aldehydes for the formation of quaternary centers

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A palladium-catalyzed benzylation of α−branched aldehydes has been developed using benzyl methyl carbonates. The method gives access to congested quaternary centers in the vicinity of one of the most sensitive carbonyl functionalities and displays unprecedented generality with respect to both coupling partners. Evidences for the direct involvement of a Pd-η^3-benzyl intermediate are provided. Extension of this strategy to the γ−benzylation of α,β−unsaturated aldehydes is further demonstrated.

Introduction

The alpha benzylation of aldehydes is a reaction of great synthetic value which enables the direct construction of $C(sp^3)−C(sp^3)$ bonds and formally provides access to homobenzylic (stereo)centers which are highly prevalent in natural products and medicinally relevant compounds.[1] The aldehyde oxidation state constitutes a pivotal platform for synthetic chemists which − in contrast − to other carbonyl functionalities limits oxidation state manipulations. Nonetheless, its exalted reactivity renders α−functionalization particularly challenging. For instance, enolate-based approaches have not reached the same level of generality than the α−alkylation of the related ketones. In addition, over-alkylation or *O*-alkylation might become competing processes for traditional base-mediated approaches with benzyl halides. Cannizzaro and Tishchenko disproportionations or self-aldol condensation are also likely to occur under basic conditions.[2] With the recent explosion of organocatalytic methods, significant progress has been made in the α−benzylation of aldehydes.[3] Amongst notable examples, Melchiorre, Cozzi and Jacobsen have independently described protocols employing linear aldehydes with stabilized benzylic carbocations.[4-6] MacMillan and Melchiorre reported mechanistically distinct photocatalytic systems for the enantioselective α−benzylation of aldehydes using strongly electron-deficient arenes and heteroarenes.[7,8] Finally, List and co-workers have identified conditions enabling the use of benzyl bromides for the α−benzylation of α−arylated aldehydes.[9] All these methods provide access to α−chiral α−benzylated aldehydes with often high enantioselectivities but this is unfortunately achieved at the expense of the generality of the reaction. Indeed, even

though some of these approaches were very innovative, they imposed severe restrictions in the diversity of nucleophilic and/or electrophilic partners that could be coupled together. Importantly, none of the existing protocols is applicable to the coupling of both linear and branched aldehydes, with indifferently electron-rich and electron-poor benzyl precursors. Except from the work of List and co-workers and one isolated example from Melchiorre and co-workers, access to quaternary centers remains problematic and no examples using α−alkyl/α−alkyl aldehydes have been reported to date.[10]

To address these limitations, we first considered developing a general Pd−catalyzed benzylation of aldehydes with the anticipation that on a longer-term perspective, an enantioselective variant of this process could be conceived. Although conceptually closely related to the well-established Pd−catalyzed allylic alkylation of carbonyl compounds, this approach has not reached the same levels of mechanistic understanding and synthetic developments.[11] One of the reasons often invoked is the difficulty associated with generating the postulated π−benzyl−palladium intermediate which requires dearomatization of the electrophilic component. Elaborating on studies by Fiaud and co-workers, the Rawal and Trost groups independently reported the efficient benzylation of indoles, oxindoles and azlactones.[12-14] These robust cyclic nucleophiles were coupled using benzyl carbonates and allowed for quaternary centers to be installed. Concomitantly, Tunge has described the Pd-catalyzed benzylation of enamines generated in situ from ketones and aldehydes.[15] Despite the good yields obtained, the excess of pyrrolidine and carbonyl compounds limits the practicality of the method while the use of coumarinyl-methyl-acetates as benzyl surrogates severely restricts the scope of the reaction. Noticeably, high

enantioinductions were reported in the studies by Trost and Czabaniuk who relied on the well-defined geometry of the cyclic enolates generated in situ from the corresponding oxindoles and azlactones. At the outset of our investigations, we were cognizant of the fact that working with *linear* aldehydes would constitute a major challenge in the control of the enolate geometry and hence on the development of an enantioselective variant of a metal-catalyzed α−benzylation process. Therefore, as a first step in this direction, we decided to first develop a non-asymmetric but very general Pd−catalyzed benzylation of aldehydes.

We report herein the development of a Pd−catalyzed benzylation of α−branched alkyl/alkyl and aryl/alkyl aldehydes using electron-rich and electron-deficient benzyl carbonates to build congested α−quaternary centers. Successful extension of this methodology to the γ−benzylation of α,β−unsaturated aldehydes and preliminary mechanistic data are also presented.

Results and discussion

Our initial optimizations were performed with a challenging α−alkyl/α−alkyl aldehyde (2-methylbutanal **1a)** and 4-methoxybenzyl acetate **2a-1** as a precursor of the electrophilic component. A first test conducted with Pd(OAc)₂, *rac*-binap and Cs₂CO₃ as base in DMF resulted in no reaction (Table 1, entry 1).

Table 1 Selected optimizations
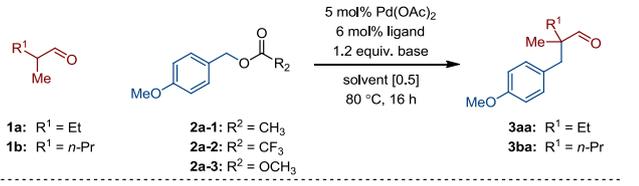
Entry	1	2	Ligand	Base	Solv.	Conv. (%)ᵃ	3 : 4 : 5
1	1a	2a-1	*rac*-binap	Cs₂CO₃	DMF	<5	−
2	1a	2a-2	*rac*-binap	Cs₂CO₃	DMF	18	3 : 2 : 1
3	1a	2a-2	*t*-Bu₃P ᵇ	Cs₂CO₃	DMF	16	0 : 1 : 2
4	1a	2a-2	Ph₃P ᵇ	Cs₂CO₃	DMF	27	0 : 5 : 1
5	1a	2a-2	*rac*-binap	Cs₂CO₃	THF	58	1 : 9 : 1
6	1a	2a-2	*rac*-binap	Cs₂CO₃	Tol.	62	1 : 10 : 1
7	1a	2a-2	*rac*-binap	Cs₂CO₃	DMA	20	2 : 2 : 1
8	1a	2a-3	*rac*-binap	Cs₂CO₃	DMF	69(55)	11 : 1 : 1
9	1a	2a-3	*rac*-binap	*i*-Pr₂NEt	DMF	<5	−
10	1a	2a-3	*rac*-binap	NaOAc	DMF	<5	−
11	1a	2a-3	*rac*-binap	Cs₂CO₃	THF	<5	−
12	1a	2a-3	*rac*-binap	Cs₂CO₃	Tol.	<5	−
13	1b	2a-3	*rac*-binap	Cs₂CO₃	DMF	62(58)ᶜ	41 : 1 : 3
14	1b	2a-3	*rac*-binap	Cs₂CO₃	DMF	80(69) ᶜ,ᵈ	48 : 1 : −

ᵃ Formation of products measured by ¹H NMR with an internal standard. Reactions on 0.4-0.5 mmol scales. Isolated yield in parenthesis. ᵇ With 10 mol% of ligand. ᶜ 100 °C, 4 h. ᵈ 2.0 equivalents of **1b**.

Traces of product **3aa** were detected when using 4-methoxybenzyl trifluoroacetate **2a-2** with concomitant formation of nominal amounts of 4-methoxybenzyl isobutyrate **4aa** and 4-methoxybenzaldehyde **5a** (entry 2). Variation of the phosphine ligand or of the solvent only led to poor conversions and an increase into the product of formal oxidative esterification **4aa** (entries 3-7). However, when 4-methoxybenzyl methyl carbonate **2a-3** was used, a significant gain in reactivity was observed and **3aa**, the product of α−benzylation, was detected as the major component (entry 8). Evaluation of other bases and solvents from this positive hit proved detrimental as catalytic activity was completely lost (entries 9-12). With the less volatile aldehyde 2-methylpentanal **1b**, the reaction temperature could be raised to 100 °C and the reaction time decreased to 4 h. Final adjustment of the stoichiometry in aldehyde (2 equiv.) afforded **3ba** in 69% yield after purification by chromatography (entry 13-14).

Table 2 Scope of α−alkyl/α−alkyl aldehydesᵃ
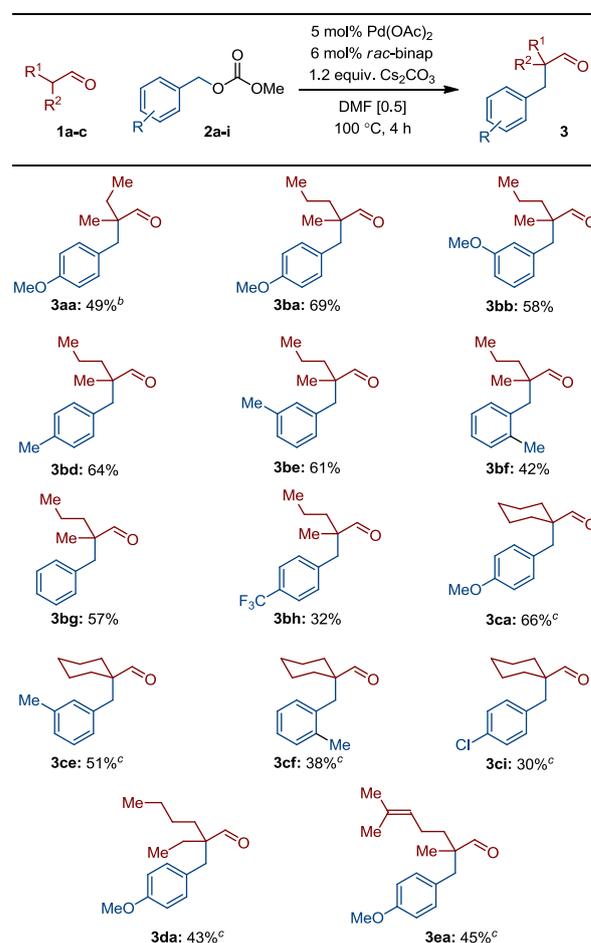
ᵃ Yield of isolated pure benzylated product for reactions conducted on 0.3-0.4 mmol scales. ᵇ 80 °C. ᶜ 100 °C, 4 h.

The scope of the reaction using α−alkyl/α−alkyl aldehydes was explored next (Table 2). For example, 2-methylpentanal **1a**, 2-methylpentanal **1b**, cyclohexane-carboxaldehyde **1c** and 2-methylhexanal **1d** could be coupled efficiently with electron-

neutral and various electron-rich *para*-, *ortho*- and *meta*-substituted benzyl methyl carbonates (11 examples; 61% average yield). In some cases, generation of the α−benzylation product was accompanied by formation of the corresponding benzaldehyde derivative, leading to a slight decrease in yield upon purification. Electron-deficient benzyl methyl carbonates were also tolerated although the corresponding α−benzylated products were isolated in much lower yields (**3bh**: 32%, **3ci**: 30%). Remarkably, perfect site selectivity was obtained when 2,6-dimethylhept-5-enal **1e** was used as nucleophilic component, affording **3ea** in 45% yield and leaving the remote olefinic moiety unreacted.[16]

Table 3 Scope of α−aryl/α−alkyl aldehydes[a]
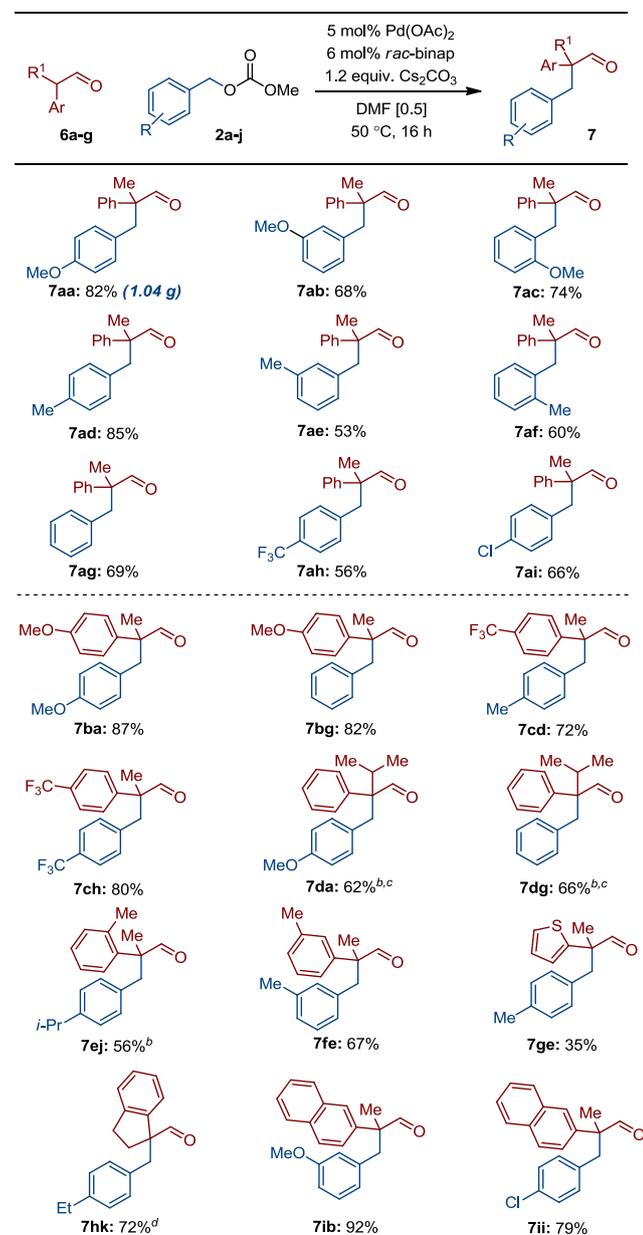
[a] Yield of isolated product for reactions conducted on a 0.3 mmol scale. [b] 100 °C. [c] 4 h. [d] 80 °C.

When testing our optimized protocol for the α−benzylation of α−aryl/α−alkyl aldehydes with 2-phenylpropanal **6a** as a representative substrate, it rapidly appeared that the reaction temperature could be decreased to 50 °C with a prolonged reaction time (16 h) while all other parameters were kept constant. The formation of ester and benzaldehyde derivatives was never observed for these cross-coupling reactions.

Systematic evaluation of the electronic demand of the electrophilic component indicated that aldehyde **6a** is particularly well-suited for α−benzylation and electron-rich, electron-neutral, electron-deficient and *ortho*-substituted benzyl methyl carbonates were all tolerated (9 examples, 68% average yield). Further variations of both coupling partners enabled all possible electronic permutations between a variety of α−aryl/α−alkyl aldehydes **6** and a representative collection of benzyl precursors **2** (see for instance: **7ba** (87%), **7cd** (72%), **7ch** (80%), **7ii** (79%)). Moreover, sterically demanding substrates were also compatible with our method as aldehydes with a secondary alkyl substituent or an *ortho*-substituted aryl moiety were cross-coupled efficiently (**7da** (62%), **7dg** (66%), **7ej** (80%), **7hk** (72%), **7ib** (92%)). Scaling up of this robust process to a gram scale was also demonstrated (**7aa**, 82%, 1.04 g).

When a particularly cumbersome substrate such as methyl 2,4,6-trimethylbenzyl carbonate **2l** was employed for the α−benzylation of **6a**, the reaction still proceeded and a mixture of 3 isomeric products was obtained (**7al**, 35% combined yield). Similarly, when the furanyl-benzyl methyl carbonate **2m** was subjected to the optimized reaction conditions, an unexpected regio-isomeric compound (**7am**) was isolated as the sole cross-coupling product (Fig. 1).[17] Although the yields of these reactions are not in the practical range, the nature and distribution of products support the existence of transient Pd−π−benzyl intermediates which equilibrate prior to nucleophilic attack and reductive elimination.
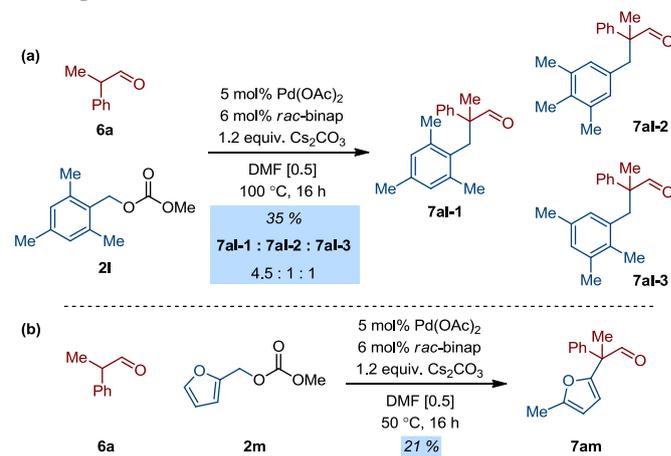
Fig. 1 Benzylation of **6a** with methyl 2,4,6-trimethylbenzyl carbonate **2l** (a) and furan-2-ylmethyl methyl carbonate **2m** (b).

Cationic benzyl-palladium complexes have been spectroscopically and structurally characterized only sporadically.[18,19] Moreover, their role as competent catalytic

entities has been demonstrated in only one case when Nettekoven and Hartwig secured that a η^3-arylethylpalladium complex was a viable intermediate in the Markovnikov hydroamination of styrenyl derivatives.[19] In the specific context of catalytic α−benzylations of carbonyl compounds, Pd−π−benzyl complexes have been generally invoked but never truly identified as potential intermediates. To remediate to this situation, we therefore carried out experiments of supporting organometallic chemistry at the stoichiometric and catalytic levels. Complex **9** was obtained as an air-stable yellow powder by reacting [(cod)PdCl$_2$] with one equivalent of freshly prepared (2-methylbenzyl)magnesium chloride at low temperature. Subsequent treatment of **9** with 1.0 equivalent of (R)-binap in dichloromethane followed by ion metathesis with 1.0 equivalent of AgOTf delivered a yellow solid of general formula [(R)-(binap)Pd(2-methylbenzyl)]OTf **10** (Fig. 2). The solution structure of **10** revealed the existence of two isomeric species in rapid equilibrium at room temperature in CD$_2$Cl$_2$ but a single species was observed in DMF-d_7. Although complete structural assignment was not possible, all spectra were consistent with a η^3-coordination of the benzyl fragment.[18] Single crystals of suitable quality for an X-ray diffraction study were obtained and a CYLview representation of **10** is disclosed on Fig. 2.[20] The salient features of this distorted square planar palladium complex are (i) the slightly longer P(1)−Pd bond distance compared to P(2)−Pd (2.3484 vs 2.2633 Å) and (ii) the much shorter Pd−C(1) bond distance than Pd−C(3) (2.124 vs 2.441 Å). This trend is similar to what has been observed for the only other structurally characterized cationic Pd-η^3-benzyl-complex supported by a chelating bisphosphine ligand.
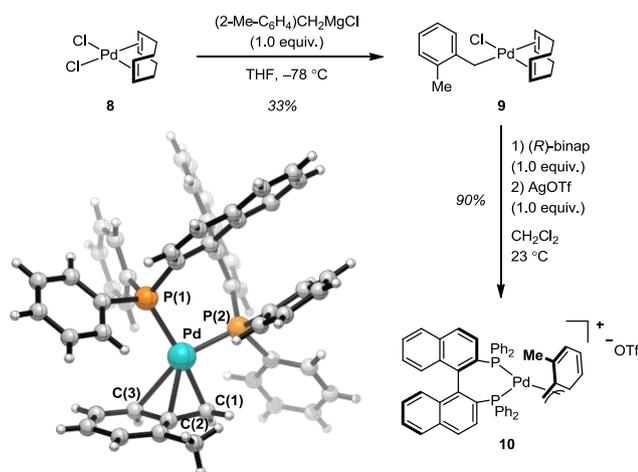
Fig. 2 Synthesis and structural characterization of [(R)-(binap)Pd-η^3-(2-methylbenzyl)]OTf **10**. Representative bond lengths (Å) and angles (°): P(1)-Pd = 2.3484(2), P(2)-Pd = 2.2633(2), Pd-C(1) = 2.124(7), Pd-C(2) = 2.274(7), Pd-C(3) = 2.441(7), P(1)-Pd-P(2) = 95.77(6).

To evaluate whether complex **10** could be a viable intermediate in the α−benzylation of α−branched aldehydes, it was engaged in a stoichiometric cross-coupling reaction using **6a** as nucleophile (Fig. 3). The corresponding product **7af** was obtained in 84% yield. Control in situ and ex situ catalytic

experiments for the coupling of **6a** with **2f** using either the Pd(OAc)$_2$/binap combination or **10** respectively displayed comparable reactivity. In the former case, **7af** was isolated in 62% yield, while in the latter it was obtained in 57% yield. Monitoring of the in situ coupling reaction by ^{31}P NMR also revealed the presence of two characteristic doublets that are consistent with the transient formation of **10** during catalysis (See ESI for details).[21] Collectively, these data strongly support the viability of **10** as a catalytically competent intermediate in the α−benzylation of α−branched aldehydes. In these experiments, all products were obtained in racemic form when (R)-binap was used as ligand. As anticipated, a major difficulty in rendering this Pd-catalyzed α−benzylation of aldehydes enantioselective will certainly be to control the geometry of the enolates with in situ deprotonation of the aldehydes.
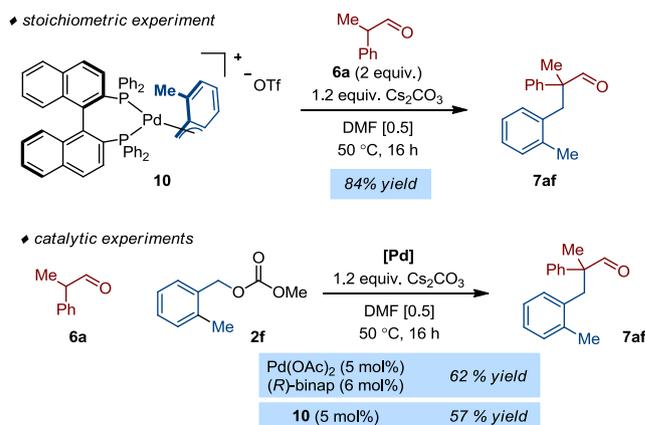
Fig. 3 Stoichiometric and catalytic experiments with complex **10** and ex situ catalytic conditions.

Table 4 γ−benzylation of aldehydes[a]
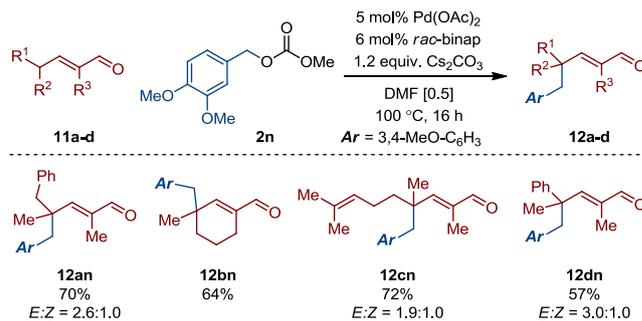
[a] On a 0.3 mmol scale with 2 equiv. of aldehyde.

Interestingly, without any variation of the optimized conditions, we found that the protocol developed for the α−benzylation of aldehydes can be directly translated to the remote γ−benzylation of γ−substituted α,β−unsaturated aldehydes (Table 4). Linear aldehydes with γ−alkyl, γ−benzyl or γ−aryl substituents and a cyclic aldehyde were all benzylated with perfect site selectivity at the γ−position using 3,4-dimethoxybenzyl methyl carbonate **2n** (57-72% yield). Although all linear substrates were geometrically pure, substantial olefin isomerization was systematically noted. This

contrasts with the results of the related γ−arylation of α,β−unsaturated aldehydes recently reported from our laboratory.[22]

Conclusions

In conclusion, we have developed a general protocol for the α− and γ−benzylations of branched aldehydes using benzyl methyl carbonates to construct quaternary centers. The reaction is tolerant to a wide variety of electronically and sterically distinct electrophilic and nucleophilic coupling partners. We have identified and structurally characterized a cationic η[3]-benzyl palladium complex that was demonstrated to be a chemically competent intermediate in the cross-coupling reaction. Current studies are aimed at developing an enantioselective version of this challenging process.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Synthetic procedures and characterizations of all compounds including copies of ^{1}H, ^{31}P{^{1}H}, and ^{13}C{^{1}H} NMR spectra. CCDC 1054603 contains the supplementary crystallographic data for this paper (compound **10**). [$C_{52}H_{41}P_2Pd$](CF_3SO_3)(CH_2Cl_2), M = 1068.18, monoclinic, a = 10.9070(3), b = 20.1115(5), c = 11.0941(3) Å, β = 99.508(3)°, V = 2400.12(11) Å3, T = 180K, space group P21 (no.4), Z = 2, 17699 reflections measured, 9439 unique (Rint = 0.0252), which were used in all calculations. Final R1 = 0.0630 and wR2 = 0.1652 (all data). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See DOI: 10.1039/b000000x/

1   (a) *Molecules and Medicine*, E. J. Corey, B. Czakò and L. Kürti eds, John Wiley & Sons, Hoboken, NJ, 2007; (b) *Classics in Stereoselective Synthesis*, E. M. Carreira and L. Kvaerno eds, Wiley-VCH, Weinheim, 2009.

2   For an excellent review, see: D. M. Hodgson and A. Charlton, *Tetrahedron*, 2014, **70**, 2207.

3   For reviews on organocatalytic methods for the α−functionalization of aldehydes, see: (a) D. W. C. MacMillan, *Nature*, 2008, **455**, 304; (b) A.-N. Alba, M. Viciano and R. Rios, *ChemCatChem*, 2009, **1**, 437; (c) P. Melchiorre, *Angew. Chem. Int. Ed.*, 2009, **48**, 1360; (d) J. Vesely and R. Rios, *ChemCatChem*, 2012, **4**, 942.

4   R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli and P. Melchiorre, *Angew. Chem. Int. Ed.*, 2008, **47**, 8707.

5   (a) P. G. Cozzi, F. Benfatti and L. Zoli, *Angew Chem. Int. Ed.*, 2009, **48**, 1313; (b) F. Benfatti, M. G. Capdevila, L. Zoli, E. Benedetto and P. G. Cozzi, *Chem. Commun.*, 2009, 5919; (c) F. Benfatti, E. Benedetto, and P. G. Cozzi, *Chem. Asian J.*, 2010, **5**, 2047.

6   A. R. Brown, W.-H. Kuo, and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2010, **132**, 9286.

7   H.-W. Shih, M. N. Vander Wal, R. L. Grange and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 13600.

8   (a) E. Arceo, I. D. Jurberg, A. Álvarez-Fernández and P. Melchiorre, *Nat. Chem.*, 2013, **5**, 750; (b) E. Arceo, A. Bahamonde, G. Bergonzini and P. Melchiorre, *Chem. Sci.*, 2014, **5**, 2438.

9   B. List, I. Čorić, O. O. Grygorenko, P. S. J. Kaib, I. Komarov, A. Lee, M. Leutzsch, S. C. Pan, A. V. Tymtsunik, and M. Van Gemmeren, *Angew. Chem. Int. Ed.*, 2014, **53**, 282.

10 For recent reviews on the construction of quaternary centers, see: (a) *Quaternary Stereocentres: Challenges and Solutions for Organic Synthesis*, J. Christoffers and A. Baro eds, Wiley-VCH: Weinheim, 2005; (b) K. Fuji, *Chem. Rev.*, 1993, **93**, 2037; (c) A. B. Dounay, L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945; (d) M. Bella, T. Gasperi, *Synlett*, 2009, **10**, 1583; (e) I. Marek, G. Sklute, *Chem. Commun.*, 2007, 1683; (f) C. Hawner, A. Alexakis, *Chem. Commun.*, 2010, **46**, 7295.

11 (a) J. D. Weaver, A. Recio III, A. J. Grenning and J. Tunge, *Chem. Rev.*, 2011, **111**, 1846; (b) B. M. Trost and L. C. Czabaniuk, *Angew. Chem. Int. Ed.*, 2014, **53**, 2826.

12 (a) J.-Y. Legros and J.-C. Fiaud, *Tetrahedron Lett.*, 1992, **33**, 2509; (b) J.-Y. Legros, M. Toffano and J.-C. Fiaud, *Tetrahedron: Asymmetry*, 1995, **6**, 1899; (c) M. Assié, J.-Y. Legros and J.-C. Fiaud, *Tetrahedron: Asymmetry*, 2005, **16**, 1183; (d) M. Assié, A. Meddour, J.-C. Fiaud and J.-Y. Legros, *Tetrahedron: Asymmetry*, 2010, **21**, 1701.

13 (a) Y. Zhu and V. H. Rawal, *J. Am. Chem. Soc.*, 2012, **134**, 111. (b) T. D. Montgomery, Y. Zhu, N. Kagawa and V. H. Rawal, *Org. Lett.*, 2013, **15**, 1140.

14 (a) B. M. Trost and L. C. Czabaniuk, *J. Am. Chem. Soc.*, 2010, **132**, 15534; (b) B. M. Trost and L. C. Czabaniuk, *J. Am. Chem. Soc.*, 2012, **134**, 5778. (c) B. M. Trost and L. C. Czabaniuk, *Chem. Eur. J.*, 2013, **19**, 15210.

15 (a) K. Cattopadhyay, A. Recio III and J. A. Tunge, *Org. Biomol. Chem.*, 2012, **10**, 6826; For related work, see: (b) R. R. P. Torregrosa, Y. Ariyarathna, K. Chattopadhyay and J. A. Tunge, *J. Am. Chem. Soc.*, 2010, **132**, 9280; (c) A. Recio, III, J. D. Heinzman and J. A. Tunge, *Chem. Commun.*, 2012, **48**, 142.

16 For examples of benzylative Heck cross-coupling reactions, see: (a) R. F. Heck and J. P. Nolley Jr., *J. Org. Chem.*, 1972, **37**, 2320; (b) G.-Z. Wu, F. Lamaty and E.-I. Negishi, *J. Org. Chem.*, 1989, **54**, 2507; (c) H. Narahashi, A. Yamamoto and I. Shimizu, *Chem. Lett.*, 2004, **33**, 348; (d) Z. Yang and J. Zhou, *J. Am. Chem. Soc.*, 2012, **134**, 11833.

17 For a related observation, see; S. Zhang, X. Yu, X. Feng, Y. Yamamoto and M. Bao, *Chem. Commun.*, 2015, **51**, 3842.

18 For structurally characterized cationic Pd-benzyl complexes, see: (a) G. Gatti, J. A. López, C. Mealli and A. Musco, *J.*

Organomet. Chem., 1994, **483**, 77; (b) F. C. Rix, M. Brookhart and P. S. White, *J. Am. Chem. Soc.*, 1996, **118**, 2436; (c) T. Murahashi, E. Mochizuki, Y. Kai and H. Kurosawa, *J. Am. Chem. Soc.*, 1999, **121**, 10660; (d) Y. Tatsumi, T. Naga, H. Nakashima, T. Murahashi and H. Kurosawa, *Chem. Commun.*, 2004, 1430; (e) C. Carfagna, G. Gatti, L. Mosca, A. Passeri, P. Paoli and A. Guerri, *Chem. Commun.*, 2007, 4540; (f) C. Carfagna, G. Gatti, P. Paoli, B. Binotti, F. Fini, A. Passeri, P. Rossi and B. Gabriele, *Organometallics*, 2014, **33**, 129.

19   U.; Nettekoven and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 1166.

20   CYLview, 1.0b; C. Y. Legault, Université de Sherbrooke, 2009 (http://www.cylview.org).

21   The 2 characteristic doublets for **10** in $^{31}P\{^{1}H\}$ resonate at 21.3 and 33.4 ppm in DMF-d_7. We believe the slight chemical shift difference observed when monitoring the reaction is likely due to the nature of the counter-ion (methoxide vs triflate) and dilution effect.

22   I. Franzoni, L. Guénée and C. Mazet, *Chem. Sci.*, 2013, **4**, 2619.