CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

## Accepted Article

**Title:** Direct Enantio- and Diastereoselective Oxidative Homo-Coupling of Aldehydes

**Authors:** Karl Anker Jørgensen, Line Næsborg, Lars Astrup Leth, Gabriel José Reyes-Rodríguez, Teresa Ann Palazzo, and Vasco Corti



**To be cited as:** *Chem. Eur. J.* 10.1002/chem.201803506

**Link to VoR:** http://dx.doi.org/10.1002/chem.201803506

Supported by
ACES

WILEY-VCH

10.1002/chem.201803506

WILEY-VCH

FULL PAPER

# Direct Enantio- and Diastereoselective Oxidative Homo-Coupling of Aldehydes

Line Næsborg, Lars A. Leth, Gabriel J. Reyes-Rodríguez, Teresa A. Palazzo, Vasco Corti, and Karl Anker Jørgensen*[a]

**Abstract:** A novel strategy for the direct enantioselective oxidative homo-coupling of α-branched aldehydes is presented. The methodology employs open-shell intermediates for the construction of chiral 1,4-dialdehydes by forming a carbon-carbon bond connecting two quaternary stereogenic centers in good yields and excellent stereoselectivities for electron-rich aromatic aldehydes. The 1,4-dialdehydes have been transformed into synthetically valuable chiral pyrrolidines. Experimental mechanistic investigations based on competition experiments combined with computational studies indicate that the reaction proceeds through a radical cation intermediate and that reactivity and stereoselectivity follow different trends.

## Introduction

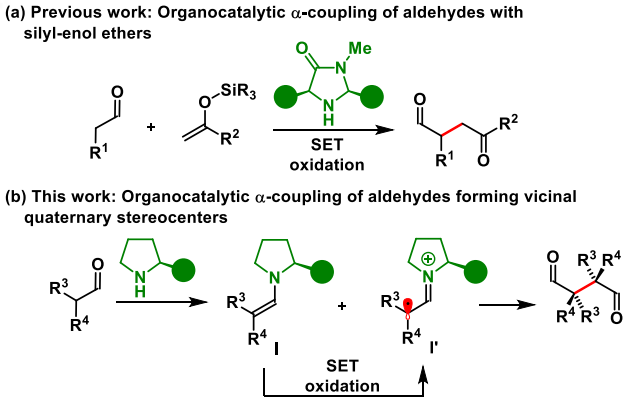
The direct stereoselective α-coupling of two carbonyl moieties into chiral 1,4-dicarbonyl compounds is a challenge due to the dual nucleophilicity of the reacting species and has, according to our knowledge, not been achieved. Indirect carbon-carbon couplings have traditionally been performed by oxidation of pre-formed enolates.[1] This elegant approach has been pursued by Baran *et al.* in the coupling of *e.g.* oxazolidinones and oxindoles with ketones applying LDA with copper(II) or iron(III).[2] Furthermore, Thomson *et al.* disclosed a related oxidative coupling of cyclic ketones *via* silyl-*bis*-enol ethers.[3] These reactions generated racemic products with low diastereoselectivitities and moderate yields. To further investigate these reactions Flowers *et al.* applied $^{7}$Li NMR to elucidate the mechanism for the oxidative coupling of lithium enolates.[4] Finally, Hirao *et al.* demonstrated that oxo-vanadium(V) induces coupling between boron- and silyl-enolates.[5]

Aldehydes are a cornerstone of organocatalysis which have been applied in HOMO and LUMO attenuating strategies and extended to SOMO activation *via* single-electron transfer (SET) using various oxidants.[6] Of particular interest, MacMillan *et al.* reported an oxidative α-coupling of aldehydes between an enamine-based radical cation and a pre-formed silyl-enol ether (Scheme 1a).[7]

An important aspect of the α-coupling of aldehydes is the potential for stereoselective construction of vicinal quaternary carbons. Strategies for the stereoselective generation of such carbon-carbon bonds are underdeveloped. Literature cites a variety of reasons for this including steric repulsion and the difficulties in selectively activating coupling partners.[2]

We envisioned a concept based on the direct coupling of α-branched aldehydes for the stereoselective construction of vicinal quaternary stereocenters in succinic 1,4-dialdehydes. An open-shell species of a catalytically generated enamine intermediate was anticipated to overcome the immense energetic hill required to form the bond connecting two quaternary stereogenic centers.[8] Herein, we disclose the first oxidative organocatalytic strategy for the diastereo- and enantioselective coupling of α-branched aldehydes (Scheme 1b).

The oxidative organocatalytic concept relies on an aldehyde condensing with an aminocatalyst forming enamine **I**, which is oxidized to generate radical cation **I'**. Intermediate **I'** is proposed to stereoselectively react with enamine-nucleophile **I** constructing a carbon-carbon bond (Scheme 1b). In the following, we present the development and scope of the catalytic α-coupling of α-branched aldehydes affording enantioenriched 1,4-dialdehydes with vicinal quaternary carbons, and their transformation into synthetically valuable chiral pyrrolidines. Mechanistic investigations *via* competition experiments and computational studies were carried out to obtain information about the reactivity and selectivity of the presented methodology.




**Scheme 1.** (a) Organocatalytic α-coupling of aldehydes with silyl-enol ethers; (b) direct organocatalytic α-coupling of aldehydes mediating the construction of vicinal quaternary stereogenic centers.

## Results and Discussion

Recently, we reported that α,β-unsaturated aldehydes undergo stereoselective γ-couplings in the presence of Cu(II), an aminocatalyst, and air ($O_2$) as terminal oxidant.[9] Under these

[a] L. Næsborg, L. A. Leth, Dr. G. J. Reyes-Rodríguez, Dr. T. A. Palazzo, V. Corti, Prof. K. A. Jørgensen
Department of Chemistry,
Aarhus University
8000 Aarhus (Denmark)
E-mail:kaj@chem.au.dk

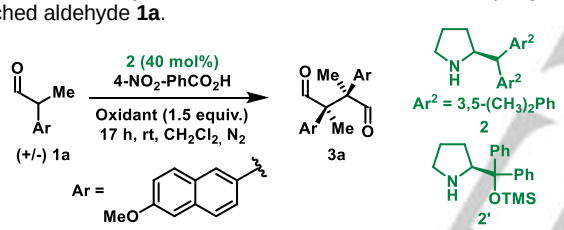
10.1002/chem.201803506




conditions linear aldehydes afford a product containing a carbon-carbon double bond connecting the two aldehydes.[10]

Encouraged by the observed reactivity, we envisioned that α-branched aldehydes might circumvent double-bond formation, allowing for the formation of vicinal quaternary carbons in a stereoselective manner. Subjecting 2-(6-methoxynaphthalen-2-yl)propanal **1a** to air/Cu(II)[9] provided 1-(6-methoxynaphthalen-2-yl)ethan-1-one as an oxidative byproduct (Table 1, entry 1). To avoid this undesired reaction, a search for different conditions was initiated applying $Ag_2CO_3$ as the oxidant with various aminocatalysts (entries 2-4). Employing $Ag_2CO_3$ increased conversion to 1,4-dialdehyde **3a**, and catalyst **2** led to superior yields and stereoselectivities. A short screening of metal salts revealed that $Ag_2CO_3$ was the optimal oxidant (entries 5, 6). Introduction of 4-$NO_2$-$PhCO_2H$ (150 mol%) led to a dramatic increase of yield and stereoselectivity (entry 7). If lower loadings of 4-$NO_2$-$PhCO_2H$ were employed, an increased amount of the oxidative byproduct 1-(6-methoxynaphthalen-2-yl)ethan-1-one was observed. Control experiments in the absence of aminocatalyst or $Ag_2CO_3$ displayed no reactivity (entries 8, 9). This screening revealed that $Ag_2CO_3$ displayed the best oxidative properties and in combination with aminocatalyst **2** (20 mol% per equiv. of **1a**) afforded **3a** in the presence of 4-$NO_2$-$PhCO_2H$ in $CH_2Cl_2$.

**Table 1.** Screening results for the oxidative homo-coupling of α-branched aldehyde **1a**.

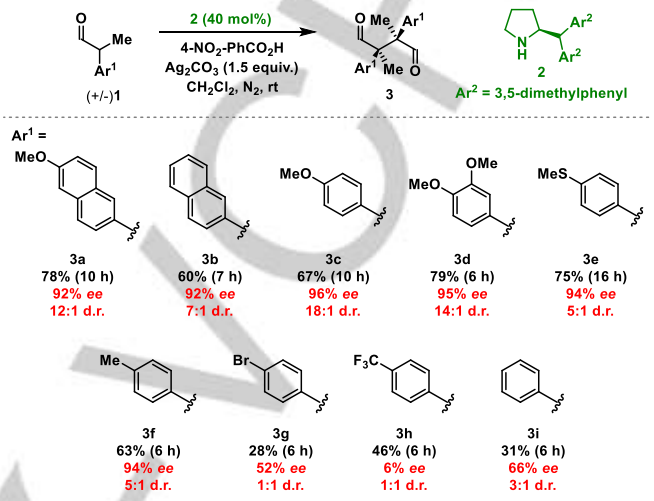



| Entry | Acid (mol%) | Oxidant | Conv. (%) | d.r. | *ee* (%) |
|---|---|---|---|---|---|
| 1[a],[b] | 0 | $Cu(OAc)_2$/air | 4 | 1:1 | - |
| 2[b] | 0 | $Ag_2CO_3$ | 90 | 1:1 | 46 |
| 3[c] | 0 | $Ag_2CO_3$ | 89 | 1:1 | 0 |
| 4 | 0 | $Ag_2CO_3$ | 96 | 2:1 | 60 |
| 5 | 0 | $AgNO_3$[d] | 27 | 2:1 | >99 |
| 6 | 0 | $FeCl_3$[d] | 0 | - | - |
| 7[e] | 150 | $Ag_2CO_3$ | >95 (78) | 7:1 | 92 |
| 8[f] | 150 | $Ag_2CO_3$ | 0 | - | - |
| 9 | 150 | - | 0 | - | - |

Reactions were carried out on a 0.05 mmol scale with 2.0 equiv. of **1a** and 40 mol% of the aminocatalyst **2** (it should be noted that this corresponds to 20 mol% per equiv. of aldehyde) in 0.4 mL of solvent. Isolated yield is given in brackets. Diastereomeric ratios are measured in the crude $^1$H NMR. [a] 20 mol% $Cu(OAc)_2$ was employed in an open-air system. [b] The catalyst **2'** was employed. [c] *L*-Proline was employed as catalyst. [d] 3 equiv. of metal salt used. [e] Reactions were carried out on a 0.1 mmol scale. [f] Control experiment performed in the absence of organocatalyst.

These optimized reaction conditions were used to investigate a representative scope of the enantioselective homo-coupling of α-branched aldehydes (Table 2).

**Table 2.** Organocatalytic enantioselective oxidative homo-coupling of α-branched aldehydes.[a]




[a] Reactions were performed on a 0.1 mmol scale. Diastereomeric ratio (d.r.) determined by $^1$H NMR after FC. Enantiomeric excess (*ee*) determined by a chiral stationary phase UPC$^2$. Absolute stereochemistry determined by analogy to X-ray crystallography analysis of **4c**·**HBr** (*vide infra*).

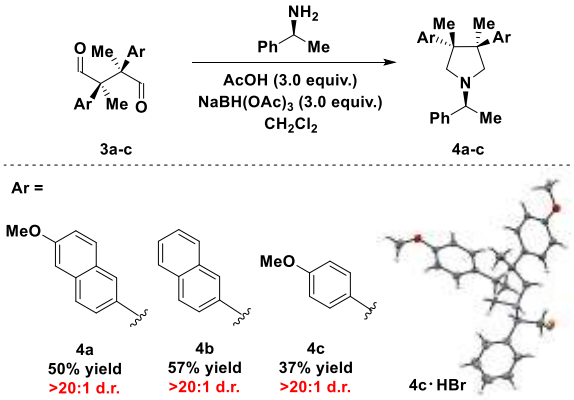
Table 2 demonstrates that the stereoselective α-coupling of electron-rich aromatic aldehydes proceeds smoothly. Reaction of an aldehyde carrying a methoxy-naphthyl moiety **1a** provided **3a** in 78% yield and excellent stereoselectivity (92% *ee*, 12:1 d.r.). It should be noted that the minor diastereoisomer is the *meso*-product. Comparable results were obtained for the naphthyl substituted aldehyde **1b**. Aldehydes with methoxy-phenyl substituents (**1c**,**d**) provided the α-coupled products **3c**,**d** in similar yields and stereoselectivities. We were pleased to observe that **3e** was obtained in 75% yield, 94% *ee* and 5:1 d.r. despite possible incompatibilities of the thioether due to potential oxidation events.[11] Furthermore, the reaction of 2-(*p*-tolyl)propanal **1f** afforded **3f** in 63% yield, 94% *ee* and 5:1 d.r. The results in entries **3g**-**i** reflect that electron-poor aromatic aldehydes are less suited for this oxidative homo-coupling as they display lower yields and stereoselectivities.

To demonstrate the synthetic potential of the 1,4-dialdehydes **3** obtained from this stereoselective coupling, reductive aminations of **3a-c** were performed (Table 3). Reaction of **3a**-**c** with (*S*)-1-phenylethan-1-amine provided the corresponding pyrrolidines **4a**-**c**. This class of interesting pyrrolidine core structures has been applied as ligands and catalysts in methodology development.[12] Additionally, pyrrolidines are privileged heterocycles in bioactive molecules.[13]

**Table 3.** Reductive amination of homo-coupling products **3a**-**c** for the formation of chiral pyrrolidines **4a**-**c**.[a]

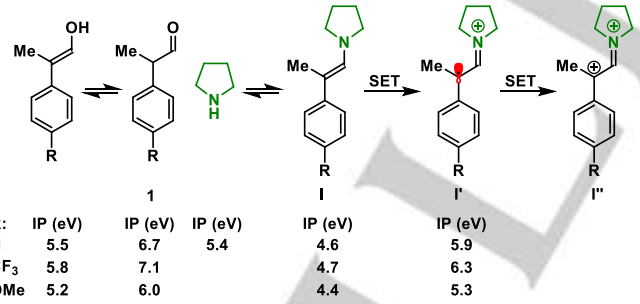
10.1002/chem.201803506
WILEY-VCH

FULL PAPER




[a] Reactions were performed on a 0.1-0.14 mmol scale. d.r. determined by $^1$H NMR after FC.

The present reaction concept allows for unprecedented enantioselective coupling of α-branched aldehydes. This methodology overcomes the difficulties in connecting two quaternary stereogenic carbons and affords the homo-coupled products in good yields and high stereoselectivities for electron-rich aldehydes. Encouraged by these results, we sought to obtain insight into the reaction mechanism to understand the factors that govern reactivity. Density functional theory (DFT) was used to determine the ionization potentials (IPs) of all relevant species (Scheme 2). The calculations support a chemoselective pathway by revealing enamine **I** to be more susceptible to oxidation than the α-branched aldehydes, enols or organocatalyst, in accordance with prior results.[6c,14] Oxidation of **I'** to a dicationic system **I''** is calculated to be higher in energy. The IPs reflect the energy required to remove one electron from the species below which they are listed. The IP values for oxidizing **I'** to **I''** are additive (*e.g.* oxidation of **I** bearing a hydrogen to **I''** requires 10.5 eV).

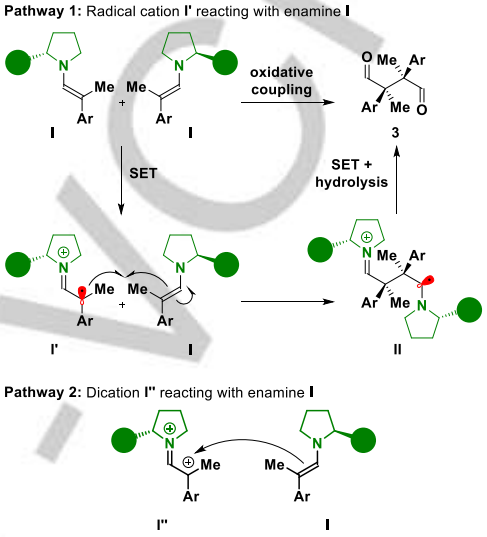



| R: | IP (eV) | IP (eV) | IP (eV) | IP (eV) | IP (eV) |
|---|---|---|---|---|---|
| H | 5.5 | 6.7 | 5.4 | 4.6 | 5.9 |
| $CF_3$ | 5.8 | 7.1 | | 4.7 | 6.3 |
| OMe | 5.2 | 6.0 | | 4.4 | 5.3 |

**Scheme 2.** Calculated IPs of α-branched aldehydes, truncated organocatalyst **2** (pyrrolidine) and intermediates.

Two conceivable reaction pathways for this oxidative coupling of α-branched aldehydes are considered: 1) radical cation **I'** reacting with neutral enamine **I**, and 2) dication **I''** reacting with neutral enamine **I** (Scheme 3).

IPs and observed reactivity could support the mechanism proposed in Pathway 1 (Scheme 3). It relies on the assumption that two equivalents of enamine **I** are formed by the reaction of the α-branched aldehyde with organocatalyst **2**. One of the formed intermediates undergoes SET-oxidation by Ag(I) generating radical cation **I'**. This intermediate is envisioned to react with enamine **I** providing adduct **II**, from which the 1,4-dialdehyde **3** is formed by subsequent SET-oxidation by Ag(I) and hydrolysis. It is also possible that an enol species reacts with an oxidized enamine **I'**. Additionally, we cannot rule out radical recombination in this mechanism, though the reaction times and product distributions might suggest radical recombination as unlikely (see Supporting Information).




**Scheme 3.** Proposed reaction mechanism (Pathway 1) and another conceivable reaction pathway for the oxidative homo-coupling of α-branched aldehydes (Pathway 2).

The following sections describe the experiments performed to obtain information discerning these two conceivable pathways, and provide insight into this oxidative homo-coupling. We set out to gain additional evidence for the proposed pathway proceeding through radical cation **I'** rather than dication **I''** (*i.e.* differentiating Pathways 1 and 2). A Newcomb radical-clock experiment could distinguish between these intermediates,[15] however, no radical-adducts were observed. Traditional kinetic methods could be employed to distinguish these pathways, unfortunately, they were not suitable due to the heterogeneity of the reaction mixture.[16] Competition experiments proved effective as a means of evaluating linear free energy relationships to discern the nature of the oxidized enamine intermediate.

We have measured relative rates of the oxidative coupling in binary mixtures of *para*-substituted 2-phenyl propanals **1** by carrying out separate experiments under the same reaction conditions. These were measured by a competitive method based on product ratios and determined by $^1$H NMR.[17-19] Relative reactivities can provide valid rate measurements given that the reaction being analysed is under kinetic control and that the competing processes are of the same kinetic order.[18,19] It should be noted that the coupling of **I** and **I'** (Scheme 3) is not proposed to be rate-determining, but product determining. The rate-determining step is likely the SET-oxidation generating **I'**, which is affected not only by the electronics of the substrate (as in the case of the calculated IPs, Scheme 2), but also by the insolubility of the oxidant.[16]

10.1002/chem.201803506


# FULL PAPER

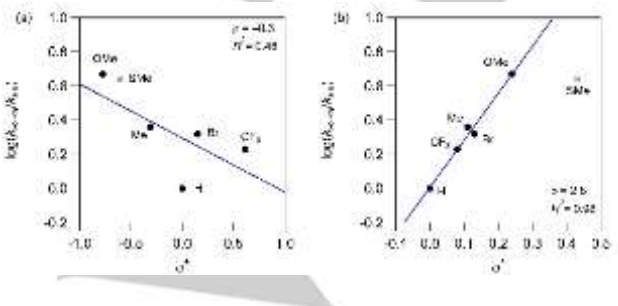
Product ratios from the competition experiments and full details regarding relative rate determination *via* direct and indirect methods can be found in the Supporting Information. The following general trend is observed: enamines having more radical-stabilizing substituents undergo faster oxidative couplings compared to their less-stabilized counterparts. *E.g.* the *para*-methoxy-substituted enamine reacts 4.7 times as fast as the unsubstituted species (Table 4, line 1). Despite the disparity in the rate- and product-determining steps, this trend is reflected by the calculated enamine IPs (**I** → **I'**, Scheme 2) in which IP(OMe)<IP(H)<IP($CF_3$).

**Table 4.** Relative reactivities of enamines $k_{R\text{-}Ph}/k_{R\text{-}Ph}$ in oxidative couplings. The values presented in italics are averages of four indirect measurements.


R = MeO (3c), MeS (3e), Me (3f), Br (3g), $F_3C$ (3h), H (3i)

| R | MeS | Me | Br | $F_3C$ | H |
|---|---|---|---|---|---|
| **MeO** | 1.2<br>*1.0±0.1* | 3.1<br>*2.4±0.8* | 2.6<br>*3.0±0.8* | 2.7<br>*3.4±0.9* | 4.7<br>*6±1* |
| **MeS** | 1 | 3.0<br>*2.1±0.3* | 2.6<br>*2.8±0.8* | 3.0<br>*3±1* | 4.4<br>*5±1* |
| **Me** | | 1 | 1.3<br>*1.1±0.3* | 1.5<br>*1.1±0.2* | 2.3<br>*2.1±0.7* |
| **Br** | | | 1 | 1.0<br>*1.1±0.1* | 2.1<br>*1.9±0.4* |
| **$F_3C$** | | | | 1 | 1.7<br>*1.7±0.3* |

The relative reactivities presented in red in Table 4 enable a Hammett analysis allowing for more specific information regarding which of the two intermediates (**I'** or **I''**) is involved.[18] Figure 1 shows four Hammett-type plots for the oxidative coupling of *para*-substituted 2-phenyl propanals **1**. Figure 1a shows poor linear correlation between log($k_{R\text{-}Ph}/k_{Ph}$) and the substituent parameter $\sigma^+$ ($R^2$ = 0.46).[20] Gratifyingly, a linear correlation between log($k_{R\text{-}Ph}/k_{Ph}$) and the substituent parameter $\sigma^{\bullet}$ was obtained ($R^2$ = 0.98, Figure 1b).[21] This supports that radical cation **I'** is the reactive species, rather than dication **I''** and distinguishes Pathways 1 and 2 (Scheme 3). In addition, the plot in Figure 1b has a value of ρ = 2.8 suggesting that the reactive intermediate **I'** is highly sensitive to substituents.[18] Despite the compatibility of thio-ether **1e** for the synthetic approach, it is excluded from the linear fit as the sulfur could be prone to participate in other oxidation events.[11] This is supported by spin-density calculations in which a large radical contribution was observed at the sulfur atom in comparison to other substrates (see Supporting Information).



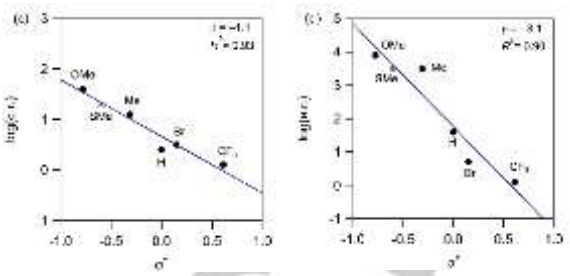


**Figure 1.** Hammett-type plots for *para*-substituted 2-phenyl propanals. (a) log($k_{R\text{-}Ph}/k_{Ph}$) *vs* $\sigma^+$ values; (b) log($k_{R\text{-}Ph}/k_{Ph}$) *vs* $\sigma^{\bullet}$ values; (c) log(d.r.) *vs* σ+ values; (d) log(e.r.) *vs* σ+ values.

The results suggest that reactivity of the homo-coupling is governed by radical stabilizing ability. Through the course of the competition experiments we found an interesting trend in stereoselectivity for the 1,4-dialdehyde products (d.r. relative to 1): MeO **3c**: 5.0±0.4 (96% *ee*); MeS **3e**: 3.7±0.7 (94% *ee*); Me **3f**: 2.9±0.6 (94% *ee*); H **3i**: 1.5±0.3 (66% *ee*); Br **3g**: 1.6±0.3 (32% *ee*); $CF_3$ **3h**: 1.15±0.06 (6% *ee*). For the electron-rich 1,4-dialdehydes **3c**,**e**,**f**, high diastereomeric ratios[22] and enantiomeric excesses were obtained, while the 1,4-dialdehyde **3h** having an electron-withdrawing substituent resulted in poor stereoselectivity. While the reactivity correlates in a linear fashion with $\sigma^{\bullet}$ values which are relative to radical stabilizing ability, the logarithm of diastereomeric and enantiomeric ratios correlate linearly with $\sigma^+$ values (Figure 1c,d).[23] These systems are mechanistically complex. The data suggest that as the electron-donating ability of the substituent increases, the energetic profile between the pathways distinguishing the two enantiomers must favor the experimentally obtained major product (*R*,*R*). This complexity might originate from the presence of an intermediate bearing both radical and cationic character.

Calculated IPs and linear free energy analysis support the claim that the homo-coupling of α-branched aldehydes occurs *via* a radical cationic intermediate. Additionally, calculated energy barriers - if located - could provide further evidence for the proposed reaction pathway. It should be noted that potential energy profiles of radical species can be challenging as they often proceed on high-energy surfaces with shallow minima.[24]

DFT (*Gaussian09*)[25] was used to calculate transition-state structures (TSSs) for the *para*-substituted 2-phenyl propanals **1c**,**f**,**g**,**h**,**i** employing the unrestricted-ωB97X-D[26] functional with a 6-31+G(d,p) basis set and the SMD solvent continuum model (see Supporting Information for details).[27] DFT, which is known to struggle with calculation of absolute barriers, can be quite useful in predicting trends. Unfortunately, all attempts at effectively modeling the trend in our relative rate ratios have been unsuccessful. Overall, it was found that **1h** having a trifluoromethyl substituent had the highest reactivity barrier and **1f** bearing a methyl substituent had the lowest barrier. Conformational analysis revealed that small changes in geometry led to significant energy differences in TSSs and intermediates, unfortunately not improving the correlation to experimental data. The relative rates account for the complete reaction conditions (*e.g.,* heterogeneity, solvated silver species, full catalyst species, etc.) which necessarily affect the energetic profile, and these

factors are not modeled by the DFT calculations. The predicted barriers, while not representative of the absolute barriers of this reaction, indicate that it is more energetically favorable for the homo-coupling reaction to occur, than for the second oxidation leading to **I''** to take place (Scheme 2).

## Conclusions

In conclusion, a novel strategy for the direct enantioselective oxidative homo-coupling of α-branched aldehydes has been developed yielding succinic 1,4-dialdehydes. These products have been transformed into synthetically valuable chiral pyrrolidines. Calculated IPs in addition to competition experiments used to construct Hammett plots support that the homo-coupling proceeds through a radical cation intermediate. Based on the mechanistic analysis, the reactivity is governed by radical character ($\sigma^{\bullet}$), while the diastereo- and enantioselectivities are influenced by cationic character ($\sigma^{+}$).

## Experimental Section

Experimental and computational details (PDF), and crystallographic data (CIF) can be found in Supporting Information.

## Acknowledgements

This work was made possible by grants from Carlsberg Foundation's 'Semper Ardens' programme, FNU, Aarhus University and DNRF. V.C. acknowledges the Alma Mater Studiorum-University of Bologna for financial support.

**Keywords:** Organocatalysis • Oxidative coupling of aldehydes • Pyrrolidines • Hammett analysis • DFT

[1] (a) M. W. Rathke, A. Lindert, *J. Am. Chem. Soc.* **1971**, *93*, 4605. (b) M. Schmittel, A. Burghart, W. Malisch, J. Reising, R. Sollner, *J. Org. Chem.* **1998**, *63*, 396. (c) P. S. Baran, M. P. DeMartino, *Angew. Chem. Int. Ed.* **2006**, *45*, 7083. (d) H.-Q. Do, H. Tran-Vu, O. Daugulis, *Organometallics* **2012**, *31*, 7816. (e) M. D. Clift, C. N. Taylor, R. J. Thomson, *Org. Lett.* **2007**, *9*, 4667. (f) Y. Kohno, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 322. (g) For relevant review, see: F. Guo, M. D. Clift, R. J. Thomson, *Eur. J. Org. Chem.* **2012**, 4881.

[2] M. P. DeMartino, K. Chen, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 11546.

[3] E. E. Robinson, R. J. Thomson, *J. Am. Chem. Soc*. **2018**, *140*, 1956.

[4] B. M. Casey, R. A. Flowers II, *J. Am. Chem. Soc.* **2011**, *133*, 11492.

[5] T. Amaya, Y. Maegawa, T. Masuda, Y. Osafune, T. Hirao, *J. Am. Chem. Soc.* **2015**, *137*, 10072.

[6] (a) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications* (Ed. P. I. Dalko), Wiley-VCH, Weinheim, **2013**. (b) B. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 13860. (c) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582.

[7] H-Y. Jang, J.-B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004.

[8] (a) J. J Murphy, D. Bastida, S. Paria, M. Fagnoni, P. Melchiorre, *Nature* **2016**, *532,* 218. (b) L. Ye, Q.-S. Gu, Y. Tian, X. Meng, G.-C. Chen, X.-Y. Liu, *Nature Comm.* **2018**, *9*, 227.

[9] L. Næsborg, V. Corti, L. A. Leth, P. H. Poulsen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2018**, *57*, 1606.

[10] S. Manna, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2016**, *55*, 5290.

[11] M. Madesclaire, *Tetrahedron* **1986**, *42*, 5459.

[12] (a) S. Cicchi, G. Ghini, L. Lascialfari, A. Brandi, F. Betti, D. Berti, S. Ferrati, P. Baglioni, *Chem. Commun.* **2007**, 1424. (b) B. S. Donslund, A. Monleón, J. Larsen, L. Ibsen, K. A. Jørgensen, *Chem. Commun*. **2015**, *51*, 13666. (c) M. Shi, Y. Satoh, T. Makihara, Y. Masaki, *Tetrahedron: Asymmetry* **1995**, *6*, 2109.

[13] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.

[14] K. Müller, F. Previdoli, H. Desilvestrio, *Helv. Chim. Acta* **1981**, *64*, 2497.

[15] M.-H. Le Tadic-Biadatti, M. Newcomb, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1467.

[16] J. J. Devery III, J. C. Conrad, D. W. C. MacMillan, R. A. Flowers II, *Angew. Chem. Int. Ed.* **2010**, *49*, 6106.

[17] R. J. Mullins, A. Vedernikov, R. Viswanathan, *J. Chem. Educ.* **2004**, *81*, 1357.

[18] E. V. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry.* University Science, Sausalito, CA, **2006**.

[19] F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry Part A: Structure and Mechanisms.* Springer, New York, NY, **2007**.

[20] (a) H. C. Brown, Y. Okamoto, *J. Am. Chem. Soc*. **1958**, *80*, 4979. (b) C. G. Swain, E. C., Jr. Lupton, *J. Am. Chem. Soc.* **1968**, *90*, 4328.

[21] X. Creary, M. E. Mehrsheikh-Mohammadi, S. McDonald, *J. Org. Chem.* **1987**, *52*, 3254.

[22] The diastereomeric ratios are slightly different from those provided in Table 1; this difference is due to that the ratios in Table 1 are obtained after flash column chromatography.

[23] (a) A. E. Wendlandt, P. Vangal, E. N. Jacobsen, *Nature* **2018**, *556*, 447. (b) S. E. Shockley, J. C. Holder, B. M. Stoltz, *Org. Lett.* **2014**, *16*, 6362.

[24] N. J. Saettel, J. Oxgaard, O. Wiest, *Eur. J. Org. Chem.* **2001**, 1429**.**

[25] Gaussian*09*, Revision B.01, M. J. Frisch *et al.*, Gaussian, Inc., Wallingford, CT, **2009** (for full *Gaussian09* reference, see Supporting Information).

[26] (a) J.-D. Chai, M. Head-Gordon, *J. Chem. Phys.* **2008**, *128*, 084106-1. (b) J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys*. **2008**, *10*, 6615. (c) M. Li, Y. Sang, X.-S. Xue, J.-P. Cheng, *Org. Chem.* **2018**, *83*, 3333.

[27] A. V. Manerich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B.*, **2009**, *113*, 6378.

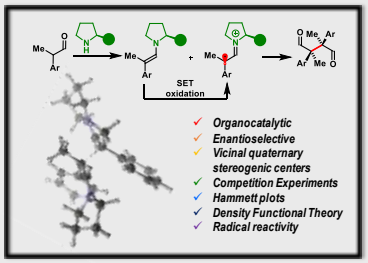
10.1002/chem.201803506

WILEY-VCH



# FULL PAPER

*Homo-coupling? That's radical!*




*L. Næsborg, L. A. Leth, G. J. Reyes-Rodríguez, T. A. Palazzo, V. Corti, and K. A. Jørgensen**

***Page No. – Page No.***
**Direct Enantio- and Diastereoselective Oxidative Homo-Coupling of Aldehydes**