


 Cite this: *Chem. Commun.*, 2024, 60, 3063

 Received 12th February 2024,
 Accepted 16th February 2024

DOI: 10.1039/d4cc00708e

rsc.li/chemcomm

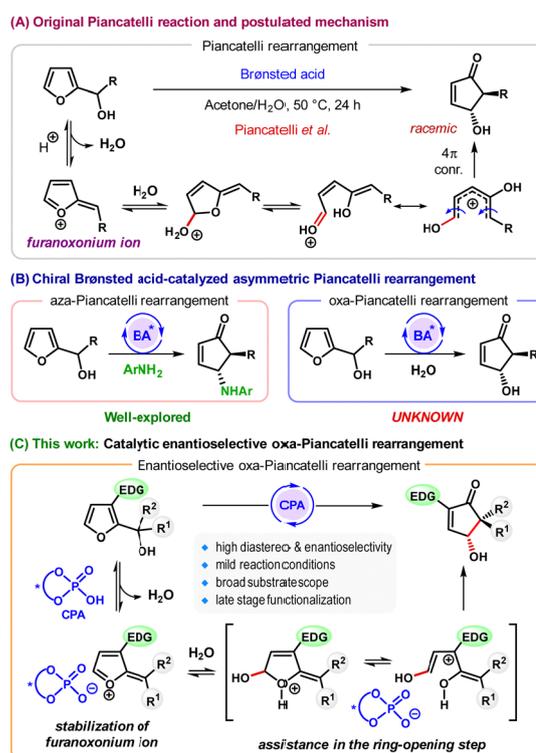
Organocatalytic enantioselective oxa-Piancatelli rearrangement†

 Rahul Sarkar, Alexander Korell and Christoph Schneider *

The first highly enantioselective oxa-Piancatelli rearrangement has been developed. This process which is catalyzed by a chiral BINOL-derived phosphoric acid rearranges a wide range of furylcarbinols into densely substituted γ -hydroxy cyclopentenones in high yield with excellent diastereo- and enantioselectivities (up to 99 : 1 er). This reaction exhibits a high functional group tolerance and was applied to complex bioactive molecules as well. The products were further manipulated into value-added molecular scaffolds further highlighting their versatility and synthetic utility.

The Piancatelli rearrangement, a unique process that directly transforms furylcarbinols into functionalized cyclopentenones, was first discovered by Piancatelli in 1976.¹ This reaction proceeds through an acid catalyzed dehydration of the furyl-2-carbinol to generate a highly reactive furanoxonium ion, which suffers nucleophilic attack of H₂O and undergoes ring-opening to form a pentadienyl cation. Subsequent conrotatory 4 π -electrocyclization provides γ -hydroxy cyclopentenones with *trans* diastereoselectivity (Scheme 1A).² The products are important molecular scaffolds, which are not only present in several natural products,³ but also serve as precursors for the synthesis of various bioactive compounds and naturally occurring molecules such as prostaglandin derivatives,^{3a,4} sibirinone,⁵ and verrillin.⁶

Significant advancements in the development of new catalytic systems, including those based on Lewis acids, have occurred over the past two decades and led to the invention of a large family of catalytic transformations involving various internal and external O-, N- and C-nucleophiles, albeit only in racemic fashion.⁷ Rueping, Sun, and Patil then independently reported the first catalytic, enantioselective processes, namely chiral Brønsted acid catalyzed enantioselective aza-Piancatelli rearrangements (Scheme 1B).⁸ For



Scheme 1 Catalytic Piancatelli rearrangement.

the original oxa-Piancatelli rearrangement, however, only a single enantioselective process has been reported to date with a chiral vanadium complex which delivers a small selection of products with generally moderate enantioselectivity.⁹

Major challenges associated with the asymmetric oxa-Piancatelli rearrangement are the attenuated nucleophilicity of H₂O in comparison to anilines¹⁰ and an undesired isomerization of the products yielding difficult to separate mixtures.^{11,12} More importantly, in comparison to the aza-Piancatelli variant, the key step of ring-opening the hemiacetal to the pentadienyl cation is significantly retarded due to the reduced resonance effect of the

Institut für Organische Chemie, Universität Leipzig, Leipzig D-04103, Germany.

E-mail: schneider@chemie.uni-leipzig.de; Fax: +49 341 97-36559;

Tel: +49 341 97-36559

 † Electronic supplementary information (ESI) available: Experimental details, characterization and analytical data. CCDC 2295678. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4cc00708e>

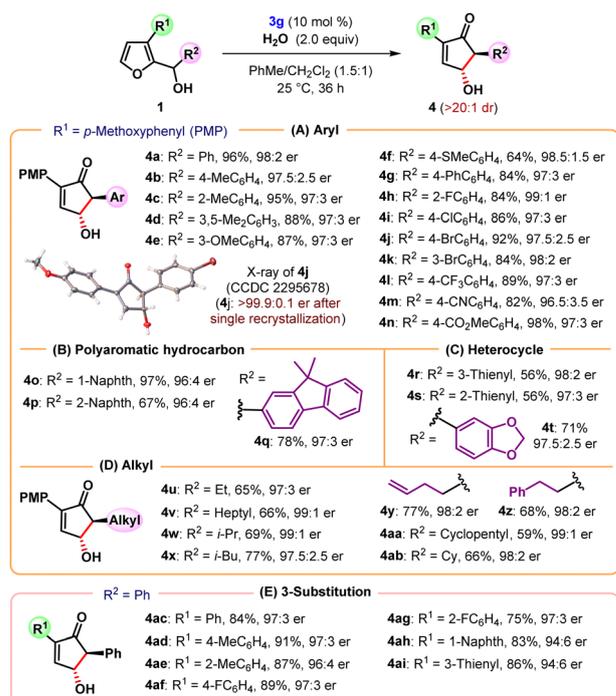

hydroxyl group.¹² Considering the importance of densely substituted and enantiomerically enriched γ -hydroxy cyclopentenones, the development of an efficient, highly enantioselective process is highly desirable.¹³

We herein report the BINOL phosphoric acid-catalyzed, highly enantioselective oxa-Piancatelli rearrangement (Scheme 1C). We envisioned that introduction of an electron-donating group at the C3 position of the furyl-2-carbinol would not only increase the stability of the *in situ* generated furanoxonium ion, but more importantly aid in the ring-opening of the hemiacetal into the pentadienyl cation through its resonance effect. The catalyst-induced 4π -electrocyclic ring closure would eventually provide the desired γ -hydroxy cyclopentenones in enantiomerically highly enriched form (Scheme 1C).

Accordingly, we began our investigations with the optimization of the catalyst and reaction conditions for *p*-methoxyphenyl (PMP) substituted secondary furyl-2-carbinol **1a** and tertiary furyl-2-carbinol **2a** in dichloromethane at 25 °C. In the presence of 10 mol% (*R*)-BINOL-derived phosphoric acid **3a** as catalyst and H₂O (2.0 equiv.) as an additive, the reaction of secondary alcohol **1a** proceeded in the expected fashion to generate the γ -hydroxy cyclopentenone **4a** with promising enantioselectivity, albeit in only a 44% yield. Similarly, tertiary alcohol **2a** also participated in the reaction under the same reaction conditions, providing the product **5a** in moderate yield with good enantioselectivity (Scheme 2). Screening of various BINOL phosphoric acids **3b–3g** and different solvents revealed that catalyst **3g** in a 1.5:1 mixture of toluene and dichloromethane as the solvent was optimal for the reaction and afforded the product **4a** in 96% isolated yield with 98:2 er (for further details, see the ESI†). In addition, the conditions optimized for **1a** were equally effective for tertiary alcohol **2a**, providing the product **5a** in 93% isolated yield with 99:1 er (Scheme 2, bottom).

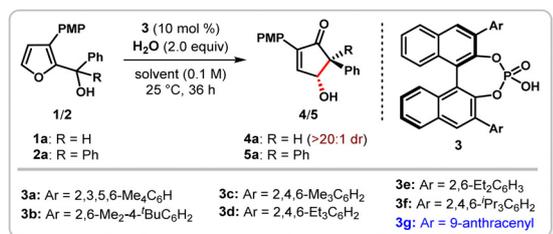
After optimizing the catalyst and reaction conditions for **1a** and **2a** (Scheme 2), we sought to test scope and limitations of this novel process (Table 1). Overall, it is quite generally applicable, and furyl-2-carbinols (**1a–1n**) bearing either electron-donating or electron-withdrawing substituents at various positions of the aryl ring at the carbinol center smoothly underwent the reaction to provide the corresponding rearranged products **4a–4n** as single diastereomers with high yields and excellent enantioselectivities (Table 1A). The relative and absolute configuration of **4j** was determined by single crystal X-ray diffraction analysis, and those

Table 1 Scope with respect to secondary furyl-2-carbinols^a



^a Reaction conditions: 0.1 mmol of **1**, 0.2 mmol of H₂O, and catalyst **3g** (10 mol%) in 1.0 mL toluene/CH₂Cl₂ (1.5:1). The diastereomeric ratio (dr) was determined by ¹H NMR of the crude reaction mixture and was >20:1 in all cases. Yields correspond to the isolated product after chromatographic purification. The er was determined by HPLC analysis on a chiral stationary phase.

of other products were assigned by analogy (CCDC 2295678; Table 1).¹⁴ Apart from simple aryl substituents, alcohols containing polyaromatic hydrocarbons **1o–1q** also effectively participated in the reaction and generated the products **4o–4q** in good yields with high er (Table 1B). Moreover, we successfully incorporated pharmaceutically relevant heterocycles into our products. For example, cyclopentenones carrying a 3-thiophenyl (**4r**), 2-thiophenyl (**4s**), and dioxolane substituent (**4t**) were obtained in moderate to good yields with excellent enantioselectivity (Table 1C). As observed by Piancatelli and coworkers, alkyl- and cycloalkyl-substituted furyl-2-carbinols are generally more resistant towards an acid catalyzed rearrangement. Thus, they typically require more drastic reaction conditions to effect the oxa-Piancatelli rearrangement or do not rearrange at all.¹⁵ To our great delight, both alkyl- and cycloalkyl substituted furyl-2-carbinols efficiently reacted under the optimized reaction conditions (Table 1D). For example, γ -hydroxy cyclopentenones containing linear (**4u** and **4v**) and branched alkyl groups (**4w** and **4x**) as well as homoallyl (**4y**) and homobenzyl (**4z**) groups were isolated with good yields and excellent enantioselectivities. Additionally, cycloalkyl substituted furyl-2-carbinols successfully participated in this reaction and gave rise to products **4aa** and **4ab** in moderate to good yields and with high enantioselectivity again. The yield of these reactions was slightly reduced compared to those with aryl-substituted carbinols likely based upon the



Scheme 2 Optimization of the reaction conditions.



attenuated resonance stabilization of the cationic intermediate. The effect of the C3-substituent on the rearrangement was also briefly investigated (Table 1E). The PMP-group could be easily replaced with a phenyl (**4ac**), *p*- and *o*-tolyl (**4ad** and **4ae**), and *p*- and *o*-fluorophenyl groups (**4af** and **4ag**) without compromising either yield or enantioselectivity. 1-Naphthyl and thiophenyl-substituted cyclopentenones **4ah** and **4ai**, however, were obtained with somewhat diminished er.

The oxa-Piancatelli rearrangement of tertiary furyl-2-carbinols was studied next (Table 2). A diverse array of tertiary carbinols carrying either electron-rich (e.g., Me, OMe, SMe, and Ph) or electron-withdrawing (e.g., Br, Cl, F, and CF₃) groups at the *meta*- and *para*-positions of the aryl ring at the carbinol center were well tolerated and provided the products **5a–5k** in uniformly high yield and with excellent enantioselectivity (Table 2A). In addition to aryl substituents, substrates **5l–5o** with polyaromatic and heterocyclic groups underwent this reaction with equal efficacy. *ortho*-Substituted diaryl alcohols failed to deliver the desired products, possibly due to severe steric congestion in the transient planar pentadienyl cation. However, unsymmetrically substituted alcohol **2p** with *o*-tolyl and phenyl groups at the carbinol center delivered cyclopentenone **5p** with a quaternary stereocenter in high yield and with 10:1 dr and 97:3 er. Likewise, tertiary furylcarbinols bearing *o*-isopropylphenyl and 1-naphthyl substituents furnished products **5r** and **5s** with excellent yields and high diastereo- and enantioselectivity. In accordance with previous reports,^{15c} tertiary furylcarbinols containing an alkyl substituent at the carbinol center were readily dehydrated to yield stable alkenes as the major products.¹⁶ Next, the scope of the

reaction was extended to tertiary furyl-2-carbinols carrying different substituents at the C3 position in place of the PMP-group (Table 2B). A range of other 2-aryl-substituted γ -hydroxy cyclopentenones **5t–5x** were obtained with generally high enantiocontrol, irrespective of the electronic nature of the aryl group. Moreover, heteroaryl residues (**5y** and **5z**) were equally effective for promoting the oxa-Piancatelli rearrangement. Intriguingly, a simple bromine substituent capable of releasing electron density into the furan ring also enabled the reaction affording the product **5aa** in high yield and with good enantioselectivity.

The mild reaction conditions of this transformation and the efficiency displayed by secondary furyl-2-carbinols **1a–1ai** allowed the use of substrates with complex bioactive residues showcasing the functional group compatibility of this process (Scheme 3). For example, furylcarbinols derived from *L*-menthol **6a**, (*S*)- β -citronellol **6b**, and geraniol **6c** smoothly participated in the oxa-Piancatelli rearrangement to generate the products **7a–7c** in high yields and with excellent diastereoselectivities (20:1 dr). Similarly, the rearrangement of **6d** and **6e** derived from (–)-borneol and (+)-fenchol, respectively, occurred efficiently to produce the corresponding cyclopentenones **7d** and **7e** with excellent yield and selectivity. *D*-Galactopyranose-derived alcohol **6f** was successfully transformed into **7f** with high diastereocontrol (>20:1 dr). Notably, such as estradiol **6g** and cholesterol **6h**, also reacted in the expected fashion to give rise to the products **7g–7h** as single diastereomers in high yields.

The scalability of our protocol was demonstrated by performing the reaction of **1a** on a 2.0 mmol scale (Scheme 4A). Under the optimal reaction conditions, product **4a** was obtained in 94% yield with the same level of enantiopurity as in the smaller scale reaction.

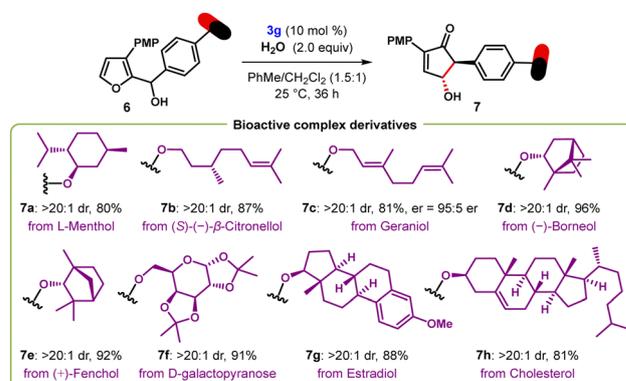
To show the synthetic utility of this process, the enantioenriched γ -hydroxy cyclopentenones were converted into synthetically useful building blocks (Scheme 4A). Toward this goal, the free hydroxy group of **4a** was protected with the TBS group to obtain the silyl ether **8** in 88% yield. Reduction of **8** with LiBH₄ in the presence of CeCl₃·7H₂O was completely regio- and diastereoselective and furnished the alcohol **9** in 64% yield. Treatment of **8** with vinylmagnesium bromide resulted in the

Table 2 Scope with respect to tertiary furyl-2-carbinols^a



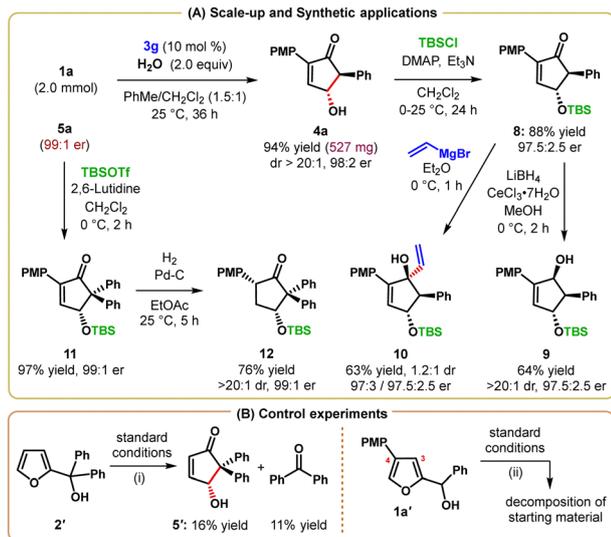
R ¹ = <i>p</i> -Methoxyphenyl (PMP) — (A) Carbinol center	
5a : R ² = Ph, 93%, 99:1 er	5g : R ² = 4-BrC ₆ H ₄ , 97%, 99:1 er
5b : R ² = 4-MeC ₆ H ₄ , 96%, 98.5:1.5 er	5h : R ² = 3-BrC ₆ H ₄ , 99%, 99:1 er
5c : R ² = 3,5-Me ₂ C ₆ H ₃ , 90%, 98:2 er	5i : R ² = 4-ClC ₆ H ₄ , 94%, 99:1 er
5d : R ² = 3-OMeC ₆ H ₄ , 88%, 98:2 er	5j : R ² = 3-FC ₆ H ₄ , 97%, 99:1 er
5e : R ² = 4-SMeC ₆ H ₄ , 83%, 98.5:1.5 er	5k : R ² = 4-CF ₃ C ₆ H ₄ , 99%, 98.5:1.5 er
5f : R ² = 4-PhC ₆ H ₄ , 96%, 99:1 er	5l : R ² = 2-Naphthyl, 94%, 99:1 er
5m : R ² = 1-Naphthyl, 82%, 98:2 er	5n : R ² = Thiophenyl, 71%, 98:2 er
5o : R ² = 2-Naphthyl, 83%, 99:1 er	
R ² = R ³ = Ph — (B) 3-Substitution	
5t : R ¹ = Ph, 89%, 98:2 er	5x : R ¹ = 2-FC ₆ H ₄ , 81%, 99:1 er
5u : R ¹ = 4-MeC ₆ H ₄ , 97%, 99:1 er	5y : R ¹ = 3-Thienyl, 93%, 97.5:2.5 er
5v : R ¹ = 4-FC ₆ H ₄ , 87%, 99:1 er	5z : R ¹ = 2-Furyl, 82%, 96.5:3.5 er
5w : R ¹ = 2-MeC ₆ H ₄ , 44%, 97.5:2.5 er	5aa : R ¹ = Br, 88%, 94:6 er

^a Reaction conditions: 0.1 mmol of **2**, 0.2 mmol of H₂O, and catalyst **3g** (10 mol%) in 1.0 mL toluene/CH₂Cl₂ (1.5:1). The dr was determined by ¹H NMR of the crude reaction mixture. Yields correspond to the isolated product after chromatographic purification. The er was determined by HPLC analysis on a chiral stationary phase.



Scheme 3 Substrates with complex bioactive residues.





Scheme 4 (A) Scale-up reaction and synthetic elaborations of γ -hydroxycyclopentenones. (B) Control experiments.

formation of tertiary alcohol **10** in 63% yield, albeit with only 1.2:1 dr. However, both diastereomers of **10** were separable through chromatographic purification. In all cases, the reactions proceeded with only minimal or no deterioration of enantiopurity. TBS-protection of **5a** using TBSOTf afforded the silyl ether **11** in 97% yield. Selective hydrogenation of the electron-deficient olefin of **11** was achieved with catalytic Pd/C, and the resulting poly-substituted cyclopentanone **12** was obtained as a single diastereomer in 76% yield.

Two control experiments with C3-unsubstituted furyl-2-carbinols were conducted under otherwise identical reaction conditions: while the secondary furyl-2-carbinol ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$) only gave rise to decomposition of the substrate, the tertiary furyl-2-carbinol **2'** ($\text{R}^1 = \text{H}$, $\text{R}^2, \text{R}^3 = \text{Ph}$) did produce the desired Piancatelli product **5'**, albeit in only 16% yield. Again, significant decomposition of starting material was observed leading to 11% of benzophenone as the only isolable side product (Scheme 4B, eqn (i)). Furthermore, shifting the *p*-methoxy-phenyl (PMP) group from C3 to the C4 position within the furan nucleus of **1a** prevented the PMP group from stabilizing the furanoxonium ion through its resonance effect. As a result, carbinol **1a'** carrying a PMP group at the C4 position failed to produce any product under standard conditions (Scheme 4B, eqn (ii)). These control experiments corroborate our initial mechanistic assumption about the role of the resonance-stabilizing C3-substituent.

In conclusion, we have developed the first catalytic, highly enantioselective oxa-Piancatelli reaction. This one-step and operationally simple process is catalyzed by a chiral BINOL-derived phosphoric acid and converts a wide range of easily accessible furyl-2-carbinols into highly valuable, substituted γ -hydroxy cyclopentenones with typically high yields and excellent levels of diastereo- and enantioselectivity. The synthetic potential of this reaction is apparent in the light of the prostaglandin class of natural products and was further demonstrated by transforming the products into other densely functionalized, chiral structural motifs.

This work was generously supported by the Deutsche Forschungsgemeinschaft (SCHN 441/16-1). We are grateful to Dr Peter Lönnecke (University of Leipzig) for the X-ray structure analysis.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- G. Piancatelli, A. Scettri and S. Barbadoro, *Tetrahedron Lett.*, 1976, **17**, 3555–3558.
- (a) M. J. Palframan and G. Pattenden, *Chem. Commun.*, 2014, **50**, 7223–7242; (b) C. Piutti and F. Quartieri, *Molecules*, 2013, **18**, 12290–12312; (c) O. Nieto Faza, C. Silva López, R. Álvarez and A. R. de Lera, *Chem. – Eur. J.*, 2004, **10**, 4324–4333.
- (a) S. P. Simeonov, J. P. M. Nunes, K. Guerra, V. B. Kurteva and C. A. M. Afonso, *Chem. Rev.*, 2016, **116**, 5744–5893; (b) S. P. Roche and D. J. Aitken, *Eur. J. Org. Chem.*, 2010, 5339–5358.
- (a) R. Katsuta, K. Aoki, A. Yajima and T. Nukada, *Tetrahedron Lett.*, 2013, **54**, 347–350; (b) J. P. Henschke, Y. Liu, X. Huang, Y. Chen, D. Meng, L. Xia, X. Wei, A. Xie, D. Li, Q. Huang, T. Sun, J. Wang, X. Gu, X. Huang, L. Wang, J. Xiao and S. Qiu, *Org. Process Res. Dev.*, 2012, **16**, 1905–1916; (c) A. R. Rodríguez and B. W. Spur, *Tetrahedron Lett.*, 2003, **44**, 7411–7415; (d) A. Rodríguez, M. Nomen, B. W. Spur and J.-J. Godfroid, *Eur. J. Org. Chem.*, 1999, 2655–2662; (e) J. H. Dygos, J. P. Adamek, K. A. Babiak, J. R. Behling, J. R. Medich, J. S. Ng and J. J. Wiczorek, *J. Org. Chem.*, 1991, **56**, 2549–2552; (f) G. Stork, C. Kowalski and G. Garcia, *J. Am. Chem. Soc.*, 1975, **97**, 3258–3260.
- D. Dobler and O. Reiser, *J. Org. Chem.*, 2016, **81**, 10357–10365.
- A. Saitman and E. A. Theodorakis, *Org. Lett.*, 2013, **15**, 2410–2413.
- Recent reviews: (a) S. Zhong, L. Xu and Y. Cai, *Synthesis*, 2022, 589–599; (b) C. Verrier, S. Moebs-Sanchez, Y. Queneau and F. Popowycz, *Org. Biomol. Chem.*, 2018, **16**, 676–687; (c) R. F. A. Gomes, J. A. S. Coelho and C. A. M. Afonso, *Chem. – Eur. J.*, 2018, **24**, 9170–9186; selected recent articles: (d) P. R. Solanke, R. Cinsani, K. Nayani, P. S. Mainkar and S. Chandrasekhar, *Chem. Commun.*, 2022, **58**, 5530–5533; (e) F. Cacheux, G. Le Goff, J. Ouazzani, J. Bignon, P. Retailleau, A. Marinetti, A. Voituriez and J.-F. Betzer, *Org. Chem. Front.*, 2021, **8**, 2449–2455; (f) S. Wang, R. Guillot, J.-F. Carpentier, Y. Sarazin, C. Bour, V. Gandon and D. Leboeuf, *Angew. Chem., Int. Ed.*, 2020, **59**, 1134–1138; (g) D. Leboeuf, L. Marin, B. Michelet, A. Perez-Luna, R. Guillot, E. Schulz and V. Gandon, *Chem. – Eur. J.*, 2016, **22**, 16165–16171; (h) D. Fisher, L. I. Palmer, J. E. Cook, J. E. Davis and J. Read de Alaniz, *Tetrahedron*, 2014, **70**, 4105–4110; (i) L. I. Palmer and J. Read de Alaniz, *Angew. Chem., Int. Ed.*, 2011, **50**, 7167–7170.
- (a) Y. Cai, Y. Tang, I. Atodiresi and M. Rueping, *Angew. Chem., Int. Ed.*, 2016, **55**, 14126–14130; (b) H. Li, R. Tong and J. Sun, *Angew. Chem., Int. Ed.*, 2016, **55**, 15125–15128; (c) A. B. Gade and N. T. Patil, *Synlett*, 2017, 1096–1100 for aza-Piancatelli rearrangements embedded into domino processes see: (d) B. Shen, Q. He, S. Dong, X. Liu and X. Feng, *Chem. Sci.*, 2020, **11**, 3862–3867; (e) L. Xu, Q. Yang, S. Zhong, H. Li, Y. Tang and Y. Cai, *Org. Lett.*, 2020, **22**, 9016–9021.
- L. Schober, M. Sako, S. Takizawa, H. Gröger and H. Sasai, *Chem. Commun.*, 2020, **56**, 10151–10154.
- (a) T. Hashimoto, Y. Shimazaki, Y. Omatsu and K. Maruoka, *Angew. Chem., Int. Ed.*, 2018, **57**, 7200–7204; (b) R. M. Demming, S. C. Hammer, B. M. Nestl, S. Gergel, S. Fademerrecht, J. Pleiss and B. Hauer, *Angew. Chem., Int. Ed.*, 2019, **58**, 173–177.
- (a) A. Scettri, G. Piancatelli, M. D'Auria and G. David, *Tetrahedron*, 1979, **35**, 135–138; (b) G. Piancatelli and A. Scettri, *Synthesis*, 1977, 116–117.
- See the ESI† Section III for details.
- These studies were inspired by our recent endeavors in ortho-quinone methide chemistry. For a recent review see: C. Dorsch and C. Schneider, *Synthesis*, 2022, 3125–3141.
- CCDC 2295678† contains the crystallographic data for **4j**.
- (a) G. Piancatelli, M. D'Auria and F. D'Onofrio, *Synthesis*, 1994, 867–889; (b) G. Piancatelli and A. Scettri, *Tetrahedron*, 1977, **33**, 69–72; (c) G. Piancatelli and A. Scettri, *Tetrahedron Lett.*, 1977, **18**, 1131–1134.
- See the ESI† for details.

