Catalytic Enantioselective Transannular Morita–Baylis–Hillman Reaction

Raquel Mato, Rubén Manzano, Efraim Reyes, Luisa Carrillo, Uxue Uria, and Jose L. Vicario

Journal of the American Chemical Society **2019** *141* (24), 9495-9499

DOI: 10.1021/jacs.9b03679

Catalytic Enantioselective Transannular Morita-Baylis-Hillman Reaction

Raquel Mato, Rubén Manzano, Efraim Reyes,* Luisa Carrillo, Uxue Uria and Jose L. Vicario*

Department of Organic Chemistry II, University of the Basque Country (UPV/EHU). P.O. Box 644, 48080 Bilbao (Spain).

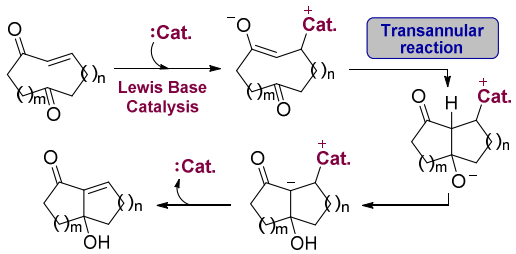
Supporting Information Placeholder

ABSTRACT: Catalytic and enantioselective approaches to transannular reactions are very limited and mostly are based on chiral Lewis acid-catalyzed pericyclic reactions. In this report we present an efficient and straightforward methodology to access bicyclic carbo- and heterocyclic scaffolds combining different ring sizes through transannular Morita-Baylis-Hillman reaction catalyzed by a chiral enantiopure bifunctional phosphine. The reaction is remarkably wide in scope and enables the use of a variety of medium- and large size ketoenone substrates leading to the final products in high yields and providing excellent stereocontrol in the formation of a quaternary stereogenic centre at the ring fusion. Moreover, its potential as a general tool in organic synthesis has been highlighted through the accomplishment of the first enantioselective total synthesis of (-)-*γ-gurjunene*, a sesquiterpene natural product.

The use of transannular reactions for building polycyclic frameworks is a significantly underdeveloped synthetic methodology in comparison with the conventional cyclization or cycloaddition approaches,[1] This can be mostly attributed to the requirement of a macrocyclic starting material, whose preparation entails a synthetic problem by itself. However, advances in synthetic methodology for the preparation of medium and large-size rings[2] has prompted several research groups to engage in the application of transannular reactions to the synthesis of complex targets, in almost all cases through diastereoselective processes that involve the use of chiral and enantioenriched starting materials.[3] In fact, catalytic and enantioselective variants of transannular reactions are limited to only four reports:[4] Jacobsen pioneered the field in 2007 with one example of a transannular Diels-Alder reaction under chiral Lewis acid catalysis[5] and two additional transition metal-catalyzed transformations were reported afterwards comprising a Claisen rearrangement[6] and an ene reaction.[7] In addition to these three cases, one single example of a catalytic and enantioselective transannular reaction under metal-free conditions has been described by List and coworkers making use of enamine catalysis.[8]

In view of the state of the art, we envisioned that a macrocyclic keto-enone substrate such as the one shown in Scheme 1 would be suitable to undergo a transannular Morita-Baylis-Hillman reaction[9] through catalytic activation by a Lewis base. Moreover, achieving enantiocontrol in the formation of the new stereogenic centre formed at the final adduct should also be possible using a chiral catalyst. There are many examples of catalytic and enantioselective versions of the Morita-Baylis-Hillman reaction in either intra- or intermolecular way,[10] which in general make use of chiral tertiary amines or phosphines as Lewis base catalysts. Even a couple of examples of diastereoselective transannular Rauhut-Currier reactions (which is regarded as the vinylogous version of the Morita-Baylis-Hillman reaction) used in the total synthesis of complex natural products have been reported,[11] but remarkably, no precedent can be found in the literature regarding a transannular Morita-Baylis-Hillman reaction either in a diastereo- or enantioselective fashion.

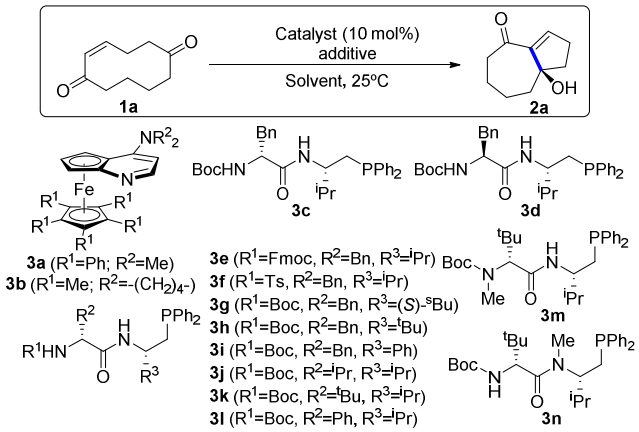
Scheme 1. The transannular Baylis-Hillman reaction.



We initially surveyed the viability of our proposal by studying the behavior of ketoenone **1a** when exposed to 4-dimethylaminopyridine (DMAP) as well-known nucleophilic catalyst for Morita-Baylis-Hillman reactions (see Table 1). As projected, bicyclic compound **2a** was isolated in a promising 65% yield after 24h (entry 1). With this result in hand, we next proceeded to survey compounds **3a** and **3b**, which are the chiral evolution of DMAP developed by Fu and coworkers.[12] Disappointingly, these catalysts did not perform well in the reaction (entries 2 and 3) and the same negative result was obtained under any other conditions tested. As a consequence, we moved to explore the performance of chiral phosphines as potential Lewis base catalysts.[13] After testing different candidates, (see supporting information for the detailed screening of catalysts) we ended up with the identification of peptide-like bifunctional phosphine **3c** as a potentially effective promoter for this transformation.[14] Remarkably, the performance of the reaction could be significantly improved through the incorporation of a protic additive, which is known to facilitate the proton transfer step required for the catalyst turnover.[15] Additional experiments led to establish that the use of a 50 mol% of phenol was optimal for the reaction to proceed with the highest possible enantiocontrol (entry 4).[16] Next, fine-tuning of the structure of the catalyst was carried out (entries 5-13), initially evaluating the possible matched/mismatched combination with respect to the absolute configuration of the two stereogenic centres present at the catalyst structure. Indeed, diastereomeric phosphine **3d** provided adduct **2a** in a similar yield but with a much lower e.e. than that provided by catalyst **3c**, working under the optimized reaction conditions (entry 5 *vs* 4). This indicates that both stereocentres play a significant role in controlling the stereochemical outcome of the reaction. Catalysts related to **3c** but with different *N*-protecting groups at the amine moiety were

surveyed (entries 6 and 7), again showing that catalyst **3c** was the best performing one in terms of enantiocontrol. Finally, we proceeded to evaluate a variety of related catalysts with different substituents at both stereocentres (entries 7-13). While substituting the side chain at the aminophosphine moiety (R^3 group) did not have any important influence on the stereocontrol (catalysts **3g-i**, entries 8-10), modifying the alkyl substituent at the aminoacid substructure (R^2 group) had a profound effect on the enantioselectivity of the process (entries 11-13), leading to an excellent 90% e.e. with the bulkiest catalyst **3k** (entry 12). Moreover, this catalyst proved to be more active than the other ones, observing complete consumption of starting material in only three hours, compared to the average of 16 hours required before. Catalysts **3m** and **3n** in which the amide NH moiety had been replaced by N-Me groups were also tested, requiring for much longer reaction time and especially providing a very poor enantioselectivity in the case of **3n**, which points towards the key role played by the NH moiety as stereodirecting element.

TABLE 1. Screening for best reaction conditions.[a]

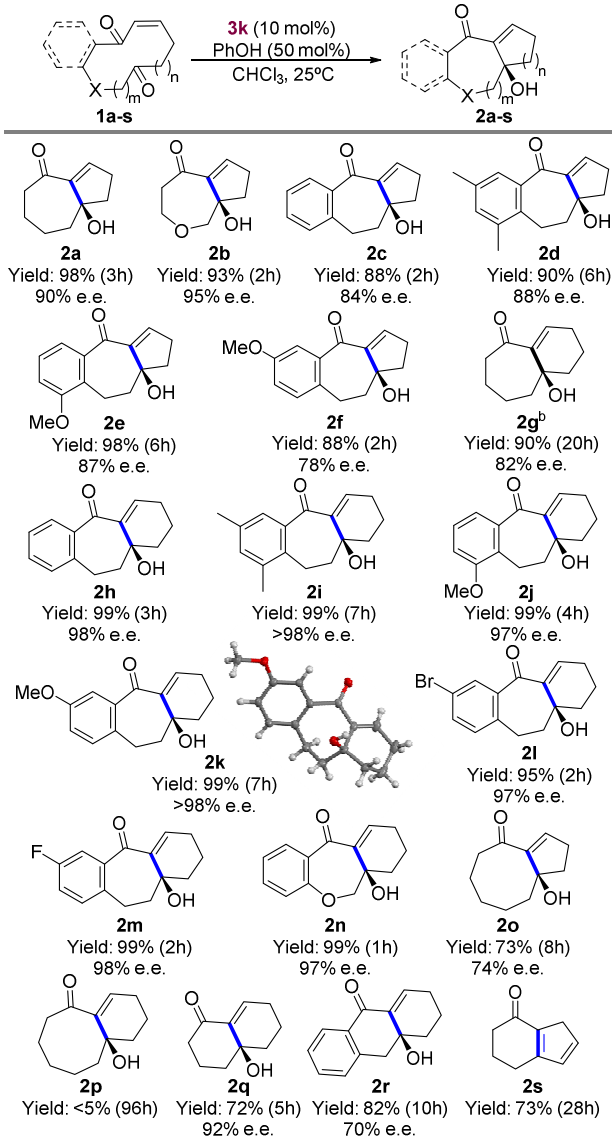


entry	Catalyst	Solvent	Additive	Time (h)	Yield (%)[b]	e.e.(%)[c]
1	DMAP	EtOH	none	24	65	
2	**3a**	EtOH	none	96	<5	n.d.[d]
3	**3b**	EtOH	none	96	<5	n.d.[d]
4	**3c**	$CHCl_3$	PhOH	16	86	84
5	**3d**	$CHCl_3$	PhOH	24	87	68
6	**3e**	$CHCl_3$	PhOH	16	77	72
7	**3f**	$CHCl_3$	PhOH	16	89	76
8	**3g**	$CHCl_3$	PhOH	16	80	84
9	**3h**	$CHCl_3$	PhOH	16	87	82
10	**3i**	$CHCl_3$	PhOH	16	99	80
11	**3j**	$CHCl_3$	PhOH	16	83	86
12	**3k**	$CHCl_3$	PhOH	3	98	90
13	**3l**	$CHCl_3$	PhOH	16	91	81
14	**3m**	$CHCl_3$	PhOH	40	82	82
15	**3n**	$CHCl_3$	PhOH	72	21	10

[a] All reactions were carried out at 0.06 mmol scale of **1a**, using 10 mol% of catalyst, 50 mol% of PhOH in 0.8 mL of $CHCl_3$ at r.t. until consumption of starting material (TLC analysis). [b]Yields refer to isolated pure product **2a**. [c] Calculated by HPLC on chiral stationary phase (see supporting information). [d] n.d. not determined.

With an optimized experimental protocol in hand, we next evaluated the scope and limitations of this transformation. As it can be seen in table 2, those substrates leading to the bicyclo[5.3.0]decane scaffold (m=1, n=1 in **1a-f**) proceeded to react efficiently, providing the corresponding adducts **2a-f** in excellent yield and e.e. The reaction worked even better with those starting materials that led to the formation of adducts with a general bicyclo[5.4.0]undecane architecture (m=1 and n=2 in **1g-n**). Moreover, substrates incorporating fused aromatic systems with different substitution patterns were also suitable for this transformation, maintaining an excellent level of enantiocontrol (see for example adducts **2c-f** and **2h-m**). The reaction also proceeds efficiently when a heteroatom is incorporated within the structure of the starting material, as exemplified with compounds **2b** and **2n**. On the contrary, the possibility of using an α,β-unsaturated lactone as substrate was also evaluated but it was found to be unreactive, presumably due to the poorer ability of the enoate moiety to act as Michael acceptor towards the catalyst.

TABLE 2. Scope of the reaction.[a]

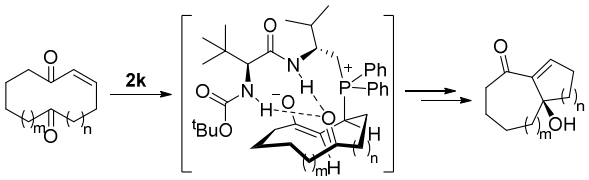


[a] All reactions were carried out at 0.20 mmol scale of **1a-t**, using 10 mol% of **3k**, 50 mol% of PhOH in 2.0 mL of $CHCl_3$ at r.t. Yields refer to isolated pure product **2a-s** and e.e. was calculated by HPLC on chiral stationary phase (See supporting information for details). [b] Reaction carried out at 0ºC in CCl_4

Those substrates that require the formation of larger ring structures at the cycloalkanone moiety of the final adduct (m>1) were found to be less reactive. In fact, a longer reaction time was required for the synthesis of the bicyclo[6.3.0]undecane scaffold (adduct **2o**), even though still providing acceptable yield and e.e. but substrate **1p** failed to undergo the desired transannular process that would eventually lead to the formation of compound **2p**. This reaction design can also be used for the construction of decalone-type scaffolds (m=0, n=2 in adducts **2q** and **2r**) but provides the corresponding dehydration product when trying to build up the bicyclo[4.3.0]nonane scaffold (m=0, n=1; substrate **1s**). Finally, we also scaled up the reaction leading to **2a**, obtaining similar results (98% yield, 90% e.e. at 2.0 mmol scale).

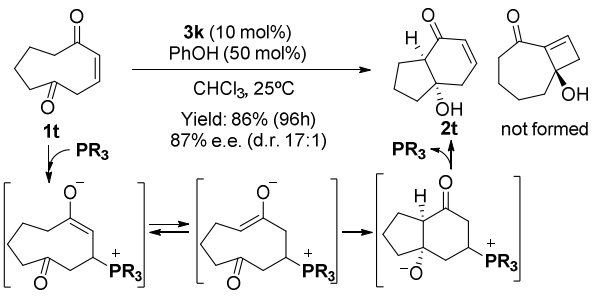
The absolute stereostructure of the adducts obtained by this protocol was established by single-crystal X-ray analysis of an enantiopure sample of compound **2k**. The configuration of all other adducts **2a-r**, was established based on mechanistic analogy. Accordingly, we can tentatively propose a model to explain the stereochemical outcome of the reaction through the formation of an intermediate such as the one depicted in Scheme 2. In this sense, once the activation of the substrate by the catalyst by conjugate addition of the phosphine has taken place, the stereodefining step would rely on the presence of H-bonding interactions between the NH moieties of the catalyst and the electrophilic ketone during the transannular aldol reaction step. This type of arrangement has also been proposed in the literature for other reactions in which his type of bifunctional phosphines have been involved.[17]

Scheme 2. Proposed stereochemical model.



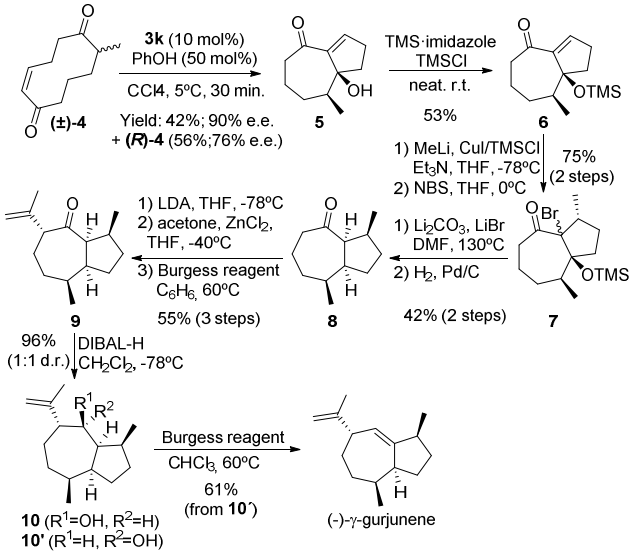
In addition, we also tested substrate **1t** (m=1, n=0 in Table 2) that should lead to the formation of a cycloheptanone structure with a fused four-membered ring. However, this compound showed a particular behavior, forming compound **2t** in an excellent yield and high enantiocontrol (see Scheme 3). The formation of this structurally different adduct can be explained by assuming isomerization of the intermediate enolate formed after the activation of the substrate. The reason for this behavior should rely on the less strained nature of **2t** in comparison with the bicyclo[5.2.0]nonane architecture expected to be formed through the conventional pathway.

Scheme 3. Proposed pathway for the formation of 2t.



Finally, we also decided to demonstrate the potential of this methodology as a general tool in total synthesis. In particular, this reaction has shown to be particularly effective for the construction of the bicyclo[5.3.0]decane structure, which is the central motif of the general architecture of many natural products of sesquiterpene and diterpene origin.[18] In particular, we focused on the application of this methodology on the synthesis of γ-gurjunene (see Scheme 4), a sesquiterpenoid natural product isolated from the gurjun balsams of several species of *Dipterocarpus*.[19] In view of its structure and observing the presence of a methyl substituent at C-4 (which is also generally found in most of the natural products with this architecture isolated up to date), we envisaged that chiral ketoenone **4** should be a very appropriate starting material. Moreover, we decided to use this substrate in a racemic form, provided that conditions were found that enable kinetic resolution during the projected catalytic enantioselective transannular Morita-Baylis-Hillman reaction. Indeed, when this compound was subjected to reaction in the presence of catalyst **3k** under slightly modified conditions,[20] bicyclic adduct **5** was isolated in 42% yield and 90% e.e. together with the resolved starting material **(*R*)-4** in 56% yield and 76% e.e.[21] Next, this adduct was protected as the corresponding TMS ether (TMS=trimethylsilyl) **6** and subsequently subjected to conjugate addition with Gilman cuprate. Disappointingly, this reaction provided the corresponding conjugate addition product with the wrong stereochemistry at the β-stereocentre. As an alternative, the enolate intermediate arising after the conjugate addition of Gilman cuprate to **6** was trapped *in situ* as the corresponding TMS enol ether, followed by treatment with *N*-bromosuccinimide (NBS), which led to the formation of brominated adduct **7**. Base-promoted elimination followed by hydrogenation provided compound **8** with the correct relative stereochemistry. The lateral 2-propenyl unit was introduced through standard aldol chemistry followed by dehydration, providing key synthetic intermediate **9** in excellent yield. Finally, installation of the endocyclic C=C double bond was accomplished by reduction of the ketone moiety followed by elimination under standard conditions, leading to the target product (-)-γ-gurjunene, whose spectroscopic and analytical data matched with those reported in the literature.[22]

Scheme 4. Total synthesis of (-)-γ-gurjunene..



In conclusion, we have established a solid and direct synthetic approach to polycyclic carbo- and heterocyclic scaffolds using transannular reactivity as an unconventional entry to this type of complex molecular architectures. Through the activation of a medium-sized ketoenone substrate with a chiral enantiopure multifunctional phosphine catalyst, a transannular Morita-Baylis-Hillman reaction takes place with excellent yield and enantioselectivity for a variety of different substrates, enabling the generation of bicyclic structures containing fused rings of different sizes and with an excellent degree of stereocontrol in the generation of the stereogenic tertiary alcohol moiety placed at the ring junction. Moreover,

this new reaction has been used as the key step in the first enantioselective total synthesis of a sesquiterpene natural product, which highlights the synthetic utility and performance of this transformation as a powerful tool in organic synthesis. For instance, the straightforward access to the hydroazulene core opens additional possibilities for the application of this methodology to other relevant examples of total synthesis. In addition, this type of reactivity will be further developed to other mechanistically related transformations in order to further widen the potential of transannular reactions as an alternative disconnection when planning the total synthesis of complex molecules.

ASSOCIATED CONTENT

Supporting Information

Survey of the performance of a variety of chiral Lewis base catalysts and additives in the model reaction. Characterization of all new compounds and copies of ^{1}H and ^{13}C NMR spectra. HPLC traces of all adducts prepared (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

AUTHOR INFORMATION

Corresponding Author

efraim.reyes@ehu.es; joseluis.vicario@ehu.es

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

The authors thank the Spanish MICINN (FEDER-CTQ2017-83633-P 52107-P) and the Basque Government (Grupos IT908-16 and fellowship to R. Mato) for financial support.

REFERENCES

(1) (a) Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. The transannular Diels-Alder strategy: applications to total synthesis. *Tetrahedron* **2001**, *57*, 4243. (b) Handa, S.; Pattenden, G. Free radical-mediated macrocyclizations and transannular cyclizations in synthesis. *Contemp. Org. Synth*. **1997**, *4*, 196. (c) Montana, A. M.; Batalla, C.; Barcia, J. A. Intramolecular haloetherification and transannular hydroxycyclization of alkenes. A synthetic methodology to obtain polycyclic ethers and amines. *Curr. Org. Chem.* **2009**, *13*, 919. (d) Rizzo, A.; Harutyunyan, S. R. Azabicycles construction: the transannular ring contraction with *N*-protected nucleophiles. *Org. Biomol. Chem.* **2014**, *12*, 6570.

(2) (a) Donald, J. R.; Unsworth, W. P. Ring-expansion reactions in the synthesis of macrocycles and medium-sized rings. *Chem. Eur. J.* **2017**, *23*, 8780. (b) Webster, A. M.; Cobb, S. L. Recent advances in the synthesis of peptoid macrocycles *Chem. Eur. J.* **2018**, *24*, 7560. (c) Josse, T.; De Winter, J.; Gerbaux, P.; Coulembier, O. Cyclic polymers by ring-closure strategies. *Angew. Chem. Int. Ed.* **2016**, *55*, 13944. (d) Hussain, A.; Youssuf, S. K.; Mukherjee, D. Importance and synthesis of benzannulated medium-sized and macrocyclic rings. *RSC Adv*. **2014**, *4*, 43241. (e) White, C. J.; Yudin, A. K. Contemporary strategies for peptide macrocyclization. *Nat. Chem.* **2011**, *3*, 509. (f) Shiina, I. Total synthesis of natural 8- and 9-membered lactones: Recent advancements in medium-sized ring formation. *Chem. Rev*. **2007**, *107*, 239. (g) Hassan, H. M. A. Recent applications of ring-closing metathesis in the synthesis of lactams and macrolactams. *Chem. Commun*. **2010**, *46*, 9100. (h) Crane, E. A.; Scheidt, K. A. Prins-type macrocyclizations as an efficient ring-closing strategy in natural product synthesis. *Angew. Chem. Int. Ed.* **2010**, *49*, 8316. (i) Parenty, A.; Moreau, X.; Campagne, J. M. Macrolactonizations in the total synthesis of natural products. *Chem. Rev.* **2006**, *106*, 911. (j) Yet, L. Metal-mediated synthesis of medium-sized rings *Chem. Rev.* **2000**, *100*, 2963. (k) Maier, M. E. Synthesis of medium-sized rings by the ring-closing metathesis reaction. *Angew. Chem. Int. Ed.* **2000**, *39*, 2073.

(3) Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. Transannular reactions in asymmetric total synthesis. *Tetrahedron* **2014**, *70*, 9461.

(4) There is one example of an enantioselective transannular aldol reaction using stoichiometric amounts of a chiral metal alkoxide as Bronsted base. Knopff, O.; Kuhne, J.; Fehr, C. Enantioselective intramolecular aldol addition/dehydration reaction of a macrocyclic diketone: Synthesis of the musk odorants (*R*)-muscone and (*R*,*Z*)-5-Muscenone. *Angew. Chem. Int. Ed*. **2007**, *46*, 1307.

(5) Balskus, E. P.; Jacobsen , E. N. Asymmetric catalysis of the transannular Diels-Alder reaction. *Science* **2007**, *317* , 1736.

(6) Jaschinski, T.; Hiersemann, M. {1,6}-Transannular Catalytic Asymmetric Gosteli–Claisen Rearrangement. *Org. Lett.* **2012**, 14, 4114.

(7) Rajapaksa, N. S.; Jacobsen, E. N. Enantioselective catalytic transannular ketone-ene reactions. *Org. Lett.* **2013**, *15*, 4238.

(8) Chandler, C. L.; List, B. Catalytic, asymmetric transannular aldolizations: Total synthesis of (+)-Hirsutene. *J. Am. Chem. Soc.* **2008**, *130*, 6737.

(9) Ciganek, E. The catalyzed α-hydroxyalkylation and α-aminoalkylation of activated olefins (the Morita-Baylis-Hillman reaction). *Org. React.* **1997**, *51*, 201.

(10) (a) Pellissier, H. Recent developments in the asymmetric organocatalytic Morita-Baylis-Hillman reaction. *Tetrahedron* **2017**, *73*, 2831. (b) Wei, Y.; Shi, M. Recent Advances in organocatalytic asymmetric Morita-Baylis-Hillman/aza-Morita-Baylis-Hillman reactions. *Chem. Rev.* **2013**, *113*, 6659. (c) Marinetti, A.; Voituriez, A. Enantioselective phosphine organocatalysis. *Synlett* **2010**, 174. (d) Masson, G.; Housseman, C.; Zhu, J. The enantioselective Morita-Baylis-Hillman reaction and its aza counterpart. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614. (e) Krishna, P. R.; Sachwani, R.; Reddy, P. S. Asymmetric Baylis-Hillman reaction: an enchanting expedition. *Synlett* **2008**, 2897. (f) Langer, P. New strategies for the development of an asymmetric version of the Baylis - Hillman reaction. *Angew. Chem. Int. Ed.* **2000**, *39*, 3049.

(11) (a) Han, J.; Li, F.; Li, C. Collective synthesis of Humulanolides using a metathesis cascade reaction. *J. Am. Chem. Soc*. **2014**, *136*, 13610. (b) Mergott, D. J.; Frank, S. A.; Roush, W. R. Total synthesis of (–)-Spinosyn A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11955. (c) Winbush, S. M.; Mergott, D. J.; Roush, W. R. Total synthesis of (−)-Spinosyn A: Examination of structural features that govern the stereoselectivity of the key transannular Diels-Alder reaction. *J. Org. Chem*. **2008**, *73*, 1818. For a seminal work on the Rauhut-Currier reaction: (d) Wang, L.-C.; Luis, A. L.; Agapiou, K., Jang, H.-Y.; Krische, M. J. Organocatalytic Michael Cycloisomerization of Bis(enones): The Intramolecular Rauhut−Currier Reaction. *J. Am. Chem. Soc*. **2002**, *124*, 2402.

(12) Fu, G. C. Asymmetric catalysis with "planar-chiral" derivatives of 4-(dimethylamino)pyridine. *Acc. Chem. Res.* **2004**, *37*, 542.

(13) Ni, H.; Chan, W.-L.; Lu, Y. Phosphine-catalyzed asymmetric organic reactions. *Chem. Rev*. **2018**, *118*, 9344.

(14) For an excellent discussion on this topic see Wei, Y.; Shi, M. Multifunctional chiral phosphine organocatalysts in catalytic asymmetric Morita-Baylis-Hillman and related reactions. *Acc. Chem. Res*. **2010**, *43*, 1005.

(15) For a complete description of the mechanism of Morita-Baylis-Hillman reaction and the role of protic additives see (a) Plata, R. E.; Singleton, D. A. A case study of the mechanism of alcohol-mediated Morita Baylis-Hillman reactions. The importance of experimental observations. *J. Am. Chem. Soc*. **2015**, *137*, 3811. (b) Isenegger, P. G.; Bachle, F.; Pfaltz, A. Asymmetric Morita-Baylis-Hillman Reaction: Catalyst development and mechanistic insights based on mass spectrometric back-reaction screening. *Chem. Eur. J.* **2016**, *22*, 17595. (c) Singh, N. K.;Satpathi, B.; Balanarayan, P.; Ramasastry S. S. V. A computational investigation of the solvent dependent enantioselective intramolecular Morita-Baylis-Hillman reaction of enones. *Org. Biomol. Chem.*, **2017**, *15*, 10212. See also (d) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. Mechanism of the Morita-Baylis-Hillman Reaction: A computational investigation. *J. Am. Chem. Soc*. **2007**, *129*, 15513.

(16) A detailed list of protic additives tested and the optimization of the amount of phenol required is included at the supporting information.

(17) Wang, T.; Han, X.; Zhong, F.; Yao, W.; Lu, Y. Amino acid-derived bifunctional phosphines for enantioselective transformations. *Acc. Chem. Res.* **2016**, *49*, 1369.

(18) Brill, Z.G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. Navigating the chiral pool in the total synthesis of complex terpene natural products. *Chem. Rev.* **2017**, *117*, 11753.

(19) (a) Ehret, C.; Ourisson, G. Le γ-gurjunene, structure et configuration: Isomerisation de l'α-gurjunene. *Tetrahedron* **1969**, *25*, 1785. (b) Rienacker, R.; Graefe, J. Catalytic transformations of sesquiterpene hydrocarbons on alkali metal/aluminum oxide. *Angew. Chem. Int. Ed.* **1985**, *24*, 320.

(20) For the complete optimization study of the kinetic resolution process (reaction time *vs* e.e.) see supporting information.

(21) The absolute stereostructure of both compounds **(*R*)-4** and **5** was determined by X-ray diffraction analysis of monocrystalline samples.

(22) Konig, G. M.; Wright, A. D. New and unusual sesquiterpenes: kelsoene, prespatane, epi-γ-gurjunene, and t-cadinthiol, from the tropical marine sponge cymbastela hooperi. *J. Org. Chem.* **1997**, *62*, 3837.

SYNOPSIS TOC