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Stereoselectivity

Probing the Mechanism of Allylic Substitution of Morita–Baylis–Hillman Acetates (MBHAs) by using the Silyl Phosphonite Paradigm: Scope and Applications of a Versatile Transformation

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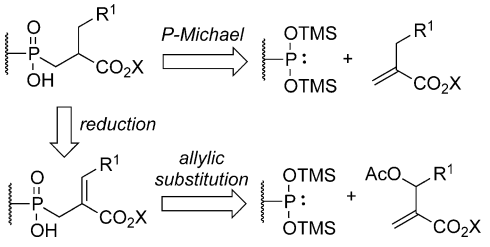
Abstract: A P–C bond-forming reaction between silyl phosphonites and Morita–Baylis–Hillman acetates (MBHAs) is explored as a general alternative towards medicinally relevant β-carboxyphosphinic structural motifs. Conversion rates of diversely substituted MBHAs to phosphinic acids **9** or **14** that were recorded by using ^{31}P NMR spectroscopy revealed unexpected reactivity differences between ester and nitrile derivatives. These kinetic profiles and DFT calculations support a mechanistic scenario in which observed differences can be explained from the "lateness" of transition states. In addition, we provide experimental evidence suggesting that enolates due to initial P-Michael addition are not formed. Based on the proposed mechanistic scenario in conjunction with DFT calculations, an interpretation of the *E*/*Z* stereoselectivity differences between ester and nitriles is proposed. Synthetic opportunities stemming from this transformation are presented, which deal with the preparation of several synthetically capricious phosphinic building blocks, whose access through the classical P-Michael synthetic route is not straightforward.

Introduction

The importance of phosphinic pseudopeptides in medicinal chemistry has been highlighted in numerous studies dealing with the potent, targeted inhibition of specific members of the Zn-metalloprotease family.[1] Such compounds have allowed us to address intricate drug-design challenges, for example, the discrimination of the N- and C-domain active sites of angiotensin I-converting enzyme (ACE-1; structures **1** and **2**, Figure 1),[2] the selective inhibition of MMP-12 (structure **3**, Figure 1),[3] and the inhibition of extra- and intracellular aminopeptidases.[4] These and other significant achievements are attributed to the special structural characteristics of the hydroxyphosphinyl group, a relatively weak zinc ligand, as compared to hydroxamic or sulfydryl-based inhibitors, whose zinc binding ability overshadows weaker but more specific enzyme–inhibitor interactions. In this context, phosphinic peptides offer opportunities for further development, given the growing effort in drug discovery to improve selectivity profiles of medicinally relevant protease inhibitors.[1b,5]

As part of our ongoing efforts to expand the structural inventory of phosphinic pseudopeptides with non-classical scaffolds potentially possessing new enzymatic activity profiles,[6] we sought for versatile alternatives to approach β-alkyl-β-carboxyphosphinic acid units that are present in most phosphinic inhibitors.[7] The most widely employed synthetic route toward such structures involves a P-Michael addition of silyl phosphonites to α,β-unsaturated esters (Scheme 1).[8] However, this



Scheme 1. Classical and proposed disconnections of β-alkyl-β-carboxyphosphinic acids.

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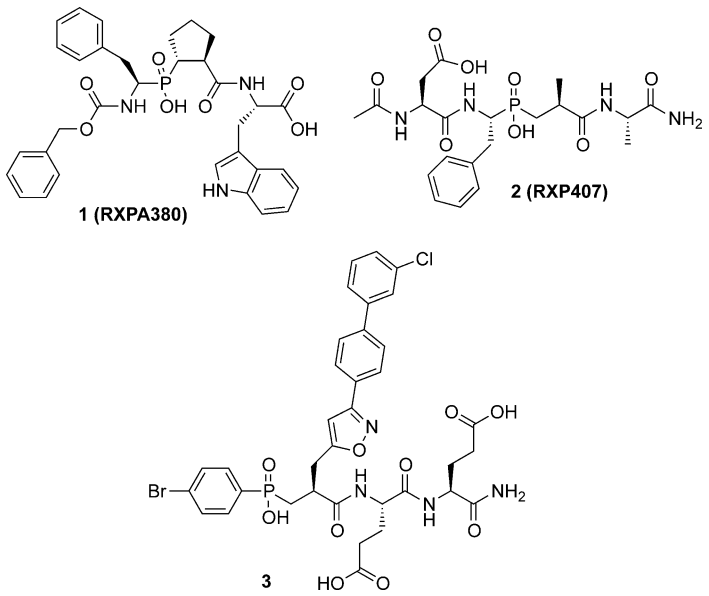


Figure 1. Examples of phosphinic Zn-metalloprotease inhibitors.

strategy suffers from inherent weaknesses that mainly involve unsuitability in cases of highly substituted pseudodipeptidic backbones, lack of general enantioselective versions of the reaction, and limited availability of functionalized starting electrophiles.

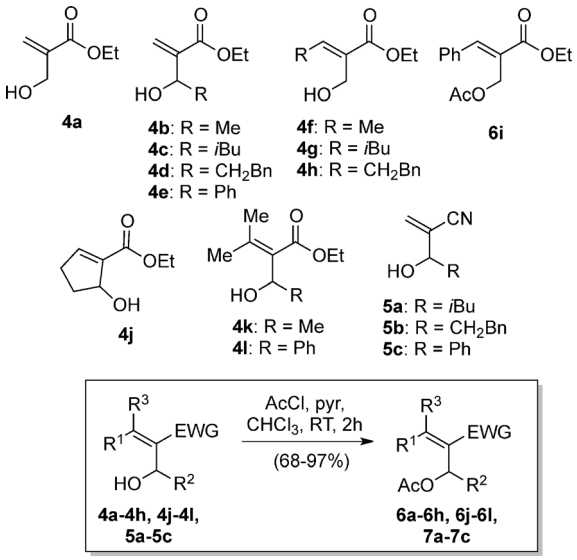
On the other hand, the versatility and ease of preparation of Morita–Baylis–Hillman (MBH) derivatives may offer a valuable alternative of broad applicability for this purpose. In general, formation of a stable P–C bond through an allylic substitution process demands a suitable trivalent phosphorus nucleophilic species that will be able to convert into a pentavalent phosphorus derivative after an Arbuzov rearrangement.[9] Janecki and co-workers observed that diethyl allyl phosphonates bearing an electron-withdrawing group at the 2-position of the allylic substituent undergo thermally induced rearrangement towards allyl phosphonates.[9b] Basavaiah et al. presented an intermolecular version of this process using the reaction of triethyl phosphite and MBH acetates (MBHAs).[9c] In 2001, ethyl (2-acetoxymethyl)acrylate was employed in a similar process with silyl phosphonites to produce pseudo-dehydroalanine phosphinic derivatives.[10] The use of silylated nucleophiles allowed the Arbuzov rearrangement to proceed at room temperature, a feature that was also employed recently by Badkar and co-workers in a similar reaction with dialkyl silyl phosphites.[11]

Prompted by the above examples of successful P–C bond formation through allylic substitution, we undertook a comprehensive study to explore the utility of silyl phosphonites as nucleophilic partners with a wide selection of MBHAs. Investigation of their reactivity profiles led us to interesting mechanistic considerations that may be applicable to other cases of allylic substitution reactions of MBHAs. These results as well as several applications of the title reaction are reported herein.

Results and Discussion

Synthesis of electrophiles 6a–l and 7a–c

A wide range of ester (**6a–l**) and nitrile MBHAs (**7a–c**) with diverse substitution patterns were prepared by typical acetylation of the parent alcohols **4a–l** and **5a–c**, respectively, with the sole exception of **6i**, which was prepared by a previously reported 1,4-diazobicyclo[2.2.2]octane (DABCO)-catalyzed acetoxy group rearrangement of isomeric acetate **6e** (Scheme 2).[12] Literature procedures based on condensation reactions between triethyl phosphonoacetate and suitable aldehydes were followed for the synthesis of allylic alcohols **4a** and **4j** (Scheme 2).[13] For compounds **4b–e** and **5a–c**, the classical MBH reaction was employed by using either ethyl acrylate (**4b–e**) or acrylonitrile (**5a–c**) as activated alkene. β-Alkyl-substituted derivatives **4f–h** were prepared starting from the allylic alcohols **4b–d** after application of the 3-step rearrangement protocol reported

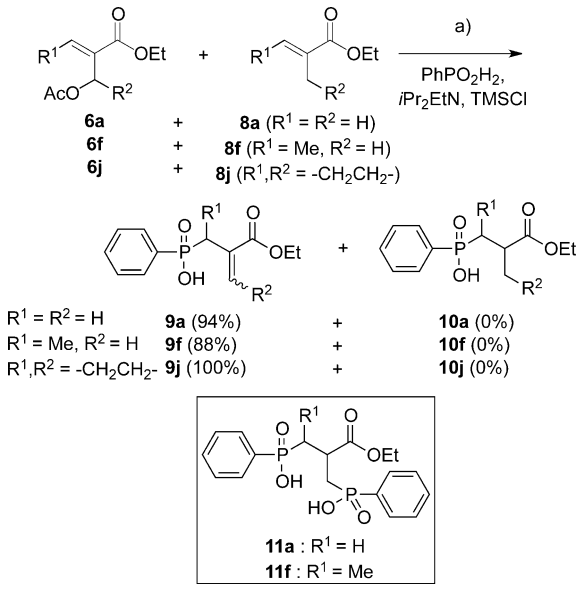


Scheme 2. Structures of MBH-type derivatives used in this study.

by Amri and co-workers.[14] The β,β-disubstituted allylic alcohol **4k** was produced in high overall yield through a $ZnCl_2$-catalyzed condensation of acetone and ethyl acetoacetate followed by Luche reduction of the resulting ketone.[15] Finally, compound **4l** was acquired after quenching a mixture of Me_2CuLi and ethyl 2-butynoate with benzaldehyde, according to the protocol of Li and co-workers (Scheme 2).[16] Details for the preparation of **6a–l** and **7a–c** are given in the Supporting Information.

Acrylates versus MBHAs in reaction with silyl phosphonites

The first data concerning the enhanced reactivity of the MBHA/silyl phosphonite system were drawn from competition



Scheme 3. Competition experiments between MBHAs **6a**, **6f**, and **6j** and the corresponding acrylates **8a**, **8f**, and **8j**. Reagents and conditions: a) iPr$_2$EtN (4 equiv), $PhPO_2H_2$ (1 equiv), **6** (1.05 equiv), **8** (1.05 equiv), TMSCl (4 equiv), CH_2Cl_2, −78 °C, then RT, 24 h, then EtOH, RT, 30 min.

experiments between MBHAs **6a**, **6f**, and **6j** and the structurally similar acrylates **8a**, **8f**, and **8j**, respectively (Scheme 3). In this respect, an excess of trimethylsilyl chloride (TMSCl) was added at −78 °C into a degassed solution containing $PhPO_2H_2$, both electrophiles (1.05 equiv of each), and Hunig's base. After stirring for 24 h at room temperature, NMR spectroscopy and MS analysis of the crude products revealed complete consumption of $PhPO_2H_2$ in all cases followed by the absence of any detectable quantities of P-Michael adducts (**10**). The fact that competition between **6j** and **8j** leads exclusively to the allylic substitution product **9j** suggests that not only the P-nucleophile exhibits an exclusive preference for MBHA **6j** over **8j**, but it also does not attack **9j**, which is a newly introduced Michael acceptor into the reaction system. These consistent observations point towards a strong lack of reactivity of P^{III} nucleophiles for β-substituted unsaturated esters such as **8j** and **9j**. Indeed, we were unable to observe any reaction between $PhPO_2H_2$ and **8j** in separate experiments, even at harsher conditions (e.g., heating in a sealed tube with HMDS as silylating agent). On the other hand, conversion of **6j** to **9j** was smoothly completed within 24 h at 0 °C, using the conditions described in Scheme 3.

A more demanding reactivity test for MBHAs involves the use of β-substituted substrates **6f** and **8f** as reacting competitors (Scheme 3). According to the conclusions drawn from the **6j**/**8j** competition experiment, silyl phosphonite is expected to react faster with **6f** than ethyl tiglate (**8f**); indeed, no **10f** was detected at the final reaction mixture. However, as the reaction proceeds the accumulation of the β-unsubstituted unsaturated ester **9f** could rise as a strong competitor for the β-substituted MBHA **6f**, stronger than **8f**. In that case, the formation of the double addition adduct **11f** could potentially be dominant. What we actually observed was the formation of **9f** as the major product (88%), whereas **11f** was limited to approximately 12% yield, judging from ^{31}P NMR spectrum. This result suggests that MBHA electrophiles are more reactive towards P^{III} nucleophiles even compared with less sterically hindered Michael acceptors.

In the case of **6a**/**8a** competition for $PhPO_2H_2$ (Scheme 3), both electrophiles and the gradually formed Michael acceptor **9a** lack a substituent at the β-position. In addition, it is known that both **6a** and **8a** can react independently with silyl phosphonites.[2b,10b] Once more, P-Michael adduct **10a** was not detected in the crude product of the competition experiment, which verifies the superiority of MBHAs over structurally similar acrylates. Unexpectedly, a small amount (≈4%) of **11a** was identified by NMR spectroscopy in the final mixture, which implies that even in a very small degree, the P-nucleophile tends to preferentially attack **9a** (precursor of **11a**) rather than **8a**, albeit both are β-unsubstituted. The exact reason for this behavior is not clear, however a possible explanation may involve the inductive effect of phosphinyl group in **9a** as compared to acrylate **8a**.

In an attempt to obtain a quantitative view of the aforementioned reactivity differences, we performed the reaction between $PhPO_2H_2$ and **6a** or **8a** in an NMR tube and followed the conversion of phosphinic acid by integration of the ^{31}P NMR spectra acquired at specific time intervals. This task was feasible due to the discrete frequencies in which silyl phosphonites (≈140 ppm) and silyl phosphinates (≈30 ppm) are resonating. From the results shown in Figure 2, a strikingly higher reactivity of **6a** is revealed: 70% conversion of $PhPO_2H_2$ by **6a** requires 3 min, whereas **8a** affords the same conversion in 31 h. Similar dramatic differences in reactivity were observed

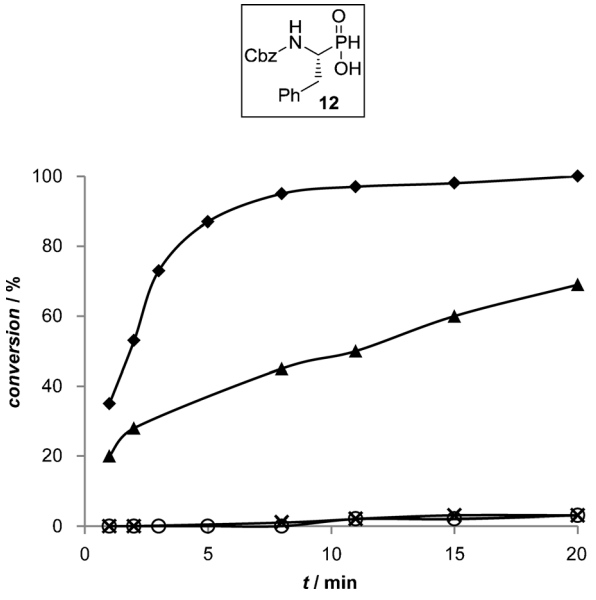


Figure 2. Conversion rates of $PhPO_2H_2$ and phosphinic acid **12** during their reaction with MBHA **6a** or acrylate **8a.** Conversion represents the ratio (product)/(product + unreacted phosphonite) as determined by ^{31}P NMR spectroscopy. Reagents and conditions: TMSCl (4 equiv), iPr$_2$EtN (4 equiv), phosphinic acid (0.95 equiv), electrophile (1 equiv), $CDCl_3$, RT. Reaction partners: $PhPO_2H_2$/**6a** (◆), $PhPO_2H_2$/**8a** (○), **12**/**6a** (▲), **12**/**8a** (×).

when aminophosphinic acid **12** was employed as the P^{III} nucleophile source, a phosphinic acid that has been extensively used for the synthesis of important phosphinic inhibitors such as **1** and **2** (Figure 1). Notably, comparison of the conversion rates of $PhPO_2H_2$ and **12** during their reaction with **6a** revealed a much lower reactivity for **12**, which could be attributed to a neighboring effect of the NH group, probably as a hydrogen donor in an intramolecular hydrogen bond as suggested previously by Smith et al. (Figure 2).[17]

Substituent effects on the reactivity of MBHAs

After the enhanced reactivity of MBHAs was established, we proceeded in comparing the effect of the substituents of MBHAs on the conversion rate of allylic substitution. To the best of our knowledge, no such comparison has been performed for any allylic substitution reaction of MBH derivatives. The silyl phosphonite/MBHA system can offer a reliable study system for this purpose since monitoring of the reaction process by ^{31}P NMR spectroscopy is straightforward.

In Figure 3, conversion rates of ester MBHAs **6a** ($R^1=R^2=H$), **6b**,**e** ($R^1=H$, $R^2\neq H$), **6h**,**i** ($R^1\neq H$, $R^2=H$), and **6j** (R^1,$R^2\neq H$) are presented. Apparently, the presence of R^1 and R^2 in the allylic

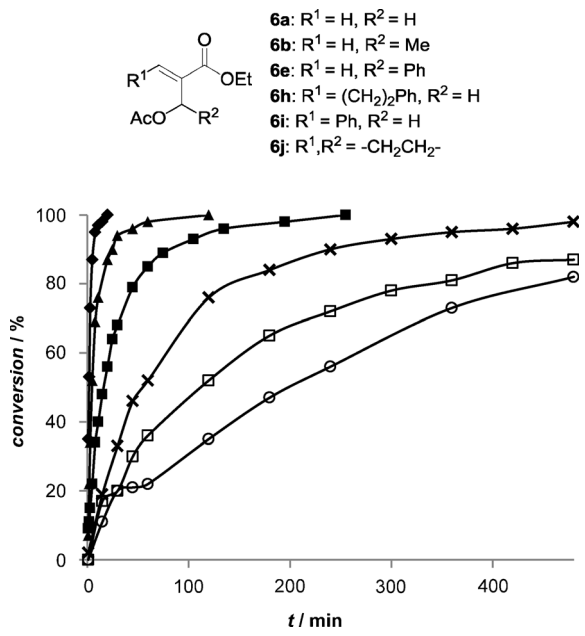


Figure 3. Conversion rates of $PhPO_2H_2$ by ester MBHAs. Conversion represents the ratio (product)/(product + unreacted phosphonite) as determined by ^{31}P NMR spectroscopy. Reagents and conditions: TMSCl (4 equiv), iPr_2EtN (4 equiv), $PhPO_2H_2$ (0.95 equiv), electrophile (1 equiv), $CDCl_3$, RT. MBHAs: **6a** (◆), **6b** (■), **6e** (▲), **6h** (×), **6i** (○), **6j** (□).

system slows down the reaction as compared with the unsubstituted MBHA **6a**. Furthermore, R^1 substituents cause a larger decrease in the conversion rate with respect to R^2 substituents (**6b**,**e** vs. **6h**,**i**), which is attributed to steric crowding on the reaction center for **6h**,**i**, but also to electronic effects induced by R^1 substituents. When both $R^1\neq H$ and $R^2\neq H$ (**6j**), conversion is even slower (**6j** vs. **6b**,**e**,**h**), except in the case of the phenyl-substituted derivative **6i**, which appears to be the least reactive MBHA in this series. This behavior for **6i** is not unexpected considering the conjugation between the phenyl group and the double bond that must be disrupted at the transition state (TS).

These observations may not be suggestive about the nature of the TS, however comparison of the conversion rates between **6b** and **6e** is more informative. As shown in Figure 3, compound **6b** is fully converted ≈6 times slower than **6e** and ≈12 times slower than the unsubstituted MBHA **6a**, which clearly shows that TS stabilization is affected by steric factors stemming from the bulk of R^2 group. However, the large difference in reactivity between **6b** and **6e** cannot be explained only in terms of steric hindrance: Had steric bulk been the main determinant for TS stabilization, compound **6b** bearing a Me group would display more or less similar reactivity with **6e**, which bears a Ph group at the same position. The larger stabilization of the TS in the case of **6e** may be attributed to the effect of the phenyl group that stabilizes the developing double bond through conjugation. This may imply overall that the process might be governed by a "late" TS, since its stabilization can be better correlated with structural features of the final products.[18]

In the following set of experiments, comparison of the reactivity profiles of nitriles **7b** and **7c** with those of esters **6d** and **6e** led to some very interesting results (Figure 4). In sharp contrast with the reactivity difference observed for esters **6d** and **6e**, the reaction rates for alkyl- (**7b**) and phenyl- (**7c**) substituted nitriles are comparable (the alkyl derivative **7b** reacts slightly faster). Based on the discussion for Figure 3, the similar reactivity profiles of **7b** and **7c** presented in Figure 4 do not support a "late" TS mechanistic scenario because the phenyl group of **7c** does not accelerate the allylic substitution by sta-

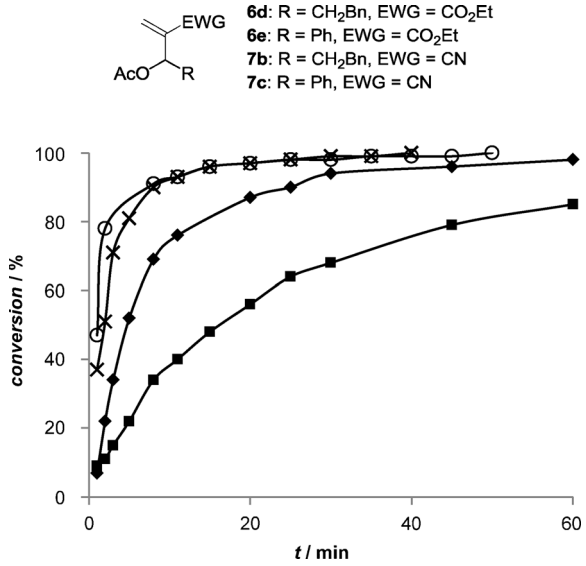


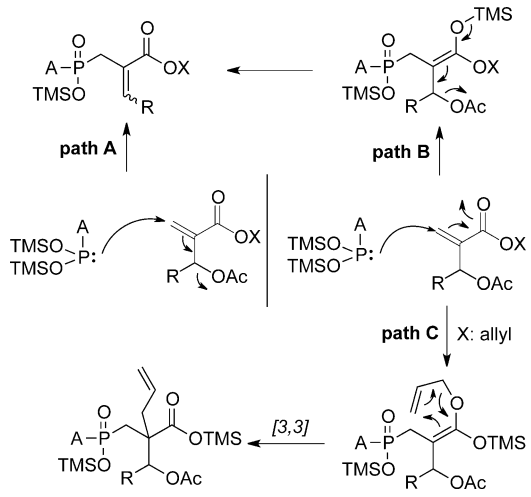
Figure 4. Conversion rates of $PhPO_2H_2$ by ester MBHAs **6d**,**e** and nitrile MBHAs **7b**,**c**. Conversion represents the ratio (product)/(product + unreacted phosphonite) as determined by using ^{31}P NMR spectroscopy. Reagents and conditions: TMSCl (4 equiv), iPr_2EtN (4 equiv), phosphinic acid (0.95 equiv), electrophile (1 equiv), $CDCl_3$, RT. MBHAs: **6d** (◆), **6e** (■), **7b** (○), **7c** (×).

bilization through conjugation, as in the case of **6e**. This means that in the case of the TS of the nitrile, double bond displacement is not advanced, which implies that the process is governed by an "earlier" TS as compared to the paradigm of the esters. This difference in the reactivity mode between structurally similar ester and nitrile MBHAs could also justify the higher conversion rates of nitriles in which structure re-organization of the MBHA at the TS is expected to be limited.

Investigation of a P-Michael addition/elimination pathway

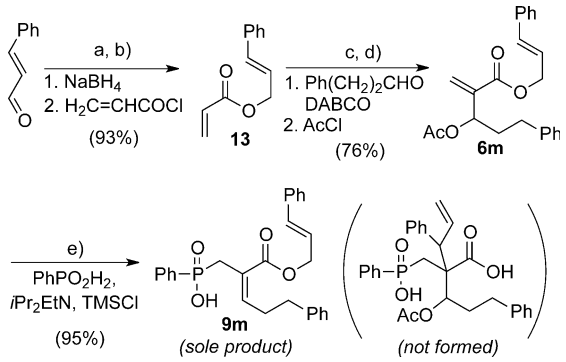
The mechanism of the S_N2' reaction has been the subject of a strong debate for more than 50 years and has been thoroughly discussed in critical reviews by Magid and later by Paquette and Stirling.[19] In our case, a synchronous mechanism in which P-addition and $^-$OAc removal processes have proceeded in the TS to comparable extents is disfavored, in line with Dewar's rule concerning the improbability of synchronous multibond reactions.[20] This is also supported by the different reactivity profiles of ester and nitrile MBHAs that suggest non-synchronous bond-forming/bond-breaking events. Concerning the concertedness of the process, a number of conflicting accounts have been reported with Bordwell's characterization of a concerted S_N2' process as a "myth" being the most controversial[21] and Houk's suggestion of a mechanism that involves "concerted attack and loss of leaving group but also a build-up of some negative charge at the central carbon of the allyl portion" standing on the opposite side.[22] Moreover, in 1996, to explain the different stereoselectivity observed during the addition of phosphites to MBHA esters and nitriles, Basavaiah et al. proposed that the reaction behaves as a P-Michael addition/elimination and that different geometries of the intermediate enolates account for the stereochemical result.[9c] More recently, Ramachandran et al. stated that allylic substitution of MBHAs was erroneously referred as an S_N2' reaction based on the experimental inability of carbanions to react with allylic acetates that are not activated at the 2-position.[23]

Following the above considerations, if a rate-determining P-Michael addition actually precedes elimination, intermediate enolates could potentially be trapped as silyl ketene acetals (Scheme 4, path B). The formation of such intermediates in a P-Michael addition has been experimentally proved in the past by using allyl acrylates and allowing the intermediate silyl ketene acetals to participate in high-yielding Ireland–Claisen rearrangements.[6a] In the same study, it has been confirmed by ^{31}P NMR spectroscopic monitoring at low temperatures that the addition of silyl phosphonites to acrylates is followed by a fast, irreversible Arbuzov-type rearrangement of the primary adducts, acting as a driving force for the formation of the intermediate silyl ketene acetals, stable at low temperatures. Based on the above, we performed an experiment aiming to trap the assumed silyl ketene acetal intermediates by an Ireland–Claisen rearrangement (Scheme 4, path C). It must be noted that Amri et al. have attempted unsuccessfully to isolate similar putative enolates as silyl ketene acetals, a failure that could be due to rapid elimination during quenching.[24]



Scheme 4. Possible mechanistic routes for the addition of silyl phosphonites to MBHAs.

The MBHA used for this experiment was designed so as to accelerate the desired Ireland–Claisen rearrangement as much as possible and at the same time to limit the probability of direct or indirect allylic substitution. For this purpose, MBHA **6m** was synthesized, as shown in Scheme 5. The choice of cinnamyl ester was based on our previous work in which an increased propensity for rearrangement in cinnamyl acrylic esters was observed.[6a] In the same study, significantly increased rates of rearrangement were also observed in the case of α-substituted acrylates, a condition that is met in **6m**. In addition, aiming to the highest possible inhibition of direct allylic substitution, based on the reactivity profiles described in Figure 3, we grafted an alkyl group at the carbon bearing the alkoxy side chain in **6m**. Despite these precautions, treatment of $PhPO_2H_2$ with **6m** under silylating conditions afforded exclusively **9m** with no traces of rearranged product even at −30 °C, at which the formation of silyl ketene acetals has been experimentally verified.[6a] This result suggests that the rate-de-



Scheme 5. Synthesis of **6m** and reaction with $PhPO_2H_2$. Reagents and conditions: a) $NaBH_4$, MeOH, RT, 15 min; b) $H_2C{=}CHCOCl$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 93% for two steps; c) $Ph(CH_2)_2CHO$, DABCO, RT, 3 d; d) AcCl, pyridine, $CHCl_3$, RT, 2 h, 76% for two steps; e) $PhPO_2H_2$, *i*Pr_2EtN, **6m**, TMSCl, CH_2Cl_2, −78 °C, then RT, 24 h, then EtOH, RT, 30 min, 95%.

termining step of the reaction does not involve enolate formation through a P-Michael addition. Such a conclusion is in accordance with the reactivity difference observed between **6b** and **6e** (Figure 3): If a rate-determining P-Michael addition was indeed preceding a rapid –OAc elimination, the effect of different substituents of **6b** and **6e** on the conversion rate would be less significant.

In an effort to shed light on the mechanism of addition of silyl phosphonites to MBHAs, we performed quantum-mechanical DFT calculations at the B3LYP/6-31G(d′) level of theory by using **6e** and **7c** as reactants. To reduce the computational cost, trimethyl phosphite, $P(OMe)_3$, was used as a nucleophile, which exhibits a similar reactivity profile according to Basavaiah.[9c] The *syn* configurations of the corresponding TSs were considered, being lower in energy than the *anti* configurations (see the Supporting Information), in accordance with previous studies by Houk and co-workers.[18,22] Comparison of several structural parameters between the reactants and the primary products (before Arbuzov rearrangement) with those of TSs obtained for **6e** ($\mathbf{TS_{6e}}$) and **7c** ($\mathbf{TS_{7c}}$) revealed striking differences in the "lateness" of the TSs (Figure 5). Considering the

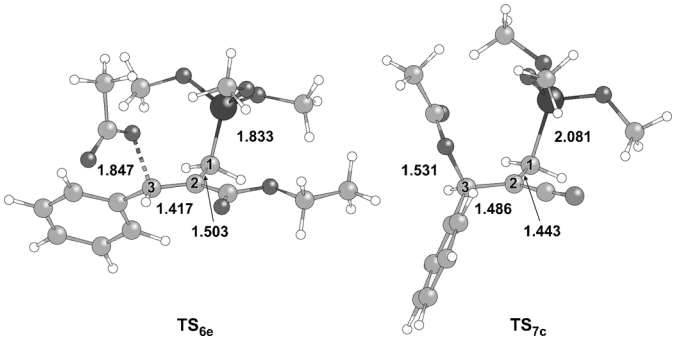


Figure 5. Structures and characteristic bond lengths of the TSs from the reaction of $P(OMe)_3$ with **6e** ($\mathbf{TS_{6e}}$) and **7c** ($\mathbf{TS_{7c}}$), calculated at the B3LYP/6-31G(d′) level of theory.

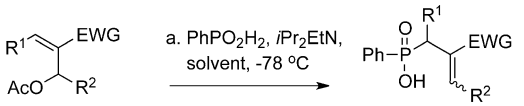
double bond displacement as an indicator of the reaction evolution on the TS, a progress of 63% was observed in the case of ester **6e**, whereas the respective value for nitrile **7c** was only 24% (see the Supporting Information). In addition, distances of nascent C^1–P and breaking C^3–O bonds support that the TS for nitrile **7c** is "reactant-like" in contrast to the TS for ester **6e** that displays more "product-like" characteristics.

Scope of the title reaction

In Table 1, the yields and *Z*/*E* ratios of ester (**9a–j**) and nitrile (**14a–c**) products are summarized.

In the case of ester MBHAs **6a** and **6f–i**, complete suppression of double-addition by-products of type **11** (Scheme 3) was not successful, as it was determined after screening of different solvents, temperatures, and reaction times. Changing the $PhPO_2H_2$/**6** ratio from 1:1.05 to 1:1.25 diminished the byproduct in all cases except for **6i**. As a compromise between limiting the starting material excess and minimizing byproduct

Table 1. Synthesis of compounds **9a–j** and **14a–c**.[a]



6a-j (EWG = CO_2Et)
7a-c (EWG = CN)

9a-j (EWG = CO_2Et)
14a-c (EWG = CN)

Entry	Starting MBHA	Method	Product	Yield [%]	*Z*/*E*[c]
1	**6a**	A	**9a**	95[b]	–
2	**6b**	B	**9b**	91	89:11
3	**6c**	B	**9c**	97	87:13
4	**6d**	B	**9d**	95	80:20
5	**6e**	B	**9e**	93	97:3
6	**6f**	A	**9f**	73	–
7	**6g**	A	**9g**	82	–
8	**6h**	A	**9h**	97	–
9	**6i**	A	**9i**	35	–
10	**6j**	A	**9j**	97	–
11	**7a**	B	**14a**	98	6:94
12	**7b**	B	**14b**	100	10:90
13	**7c**	B	**14c**	93	33:66

[a] Reagents and conditions: Method A: **6** (1.15 equiv), $PhPO_2H_2$ (1.0 equiv), *i*Pr_2EtN (4 equiv), CH_2Cl_2, −78 °C, addition of TMSCl (4 equiv), then RT, 24 h, then EtOH, RT, 30 min; Method B: **6** or **7** (1.05 equiv), $PhPO_2H_2$ (1.0 equiv), *i*Pr_2EtN (4 equiv), MeCN, −78 °C, addition of TMSCl (4 equiv), then RT, 6 h, then EtOH, RT, 30 min. [b] Reaction time: 2 h. [c] Determined by the ^{1}H NMR chemical shift of the vinylic protons that resonate at typical frequencies, according to the literature.[9b,c,f,11,25]

yield, we settled on a $PhPO_2H_2$/**6** = 1:1.15 ratio leading to final yields as listed in Table 1. For esters **6b–e** and nitriles **7a–c**, we focused our attention on stereoselectivity. In most of the cases, high stereoselectivities were observed that were not significantly altered by temperature variations. On the other hand, *Z*/*E* ratio of the final alkenes seems to be slightly influenced by the nature of the solvent. In particular, toluene or THF resulted in lower stereoselectivities for **6c** (*Z*/*E* = 72:28 and 78:22, respectively) as compared with CH_2Cl_2 (*Z*/*E* = 83:17) and MeCN or DMF (*Z*/*E* = 87:13 for both). Not unexpectedly, the β,β-disubstituted MBHAs **6k** and **6l** proved completely unreactive under the reported or harsher reaction conditions. This lack of reactivity was not surpassed even when trifluoroacetates were used as electrophiles instead of acetates.

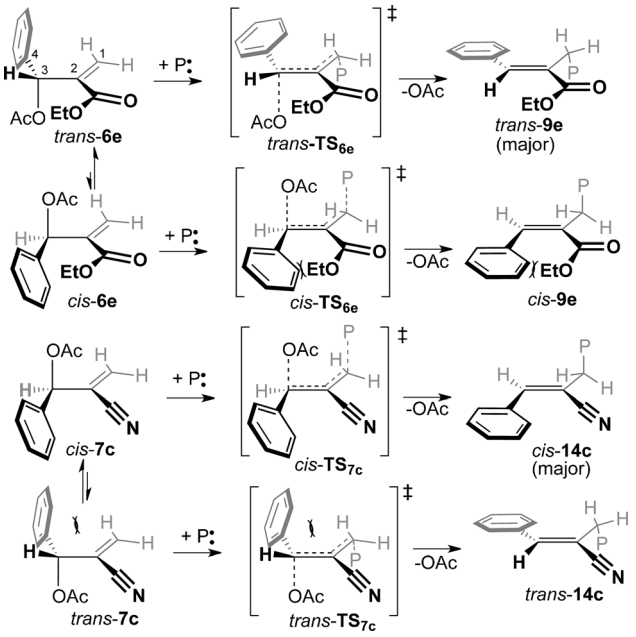
Stereoselectivity and mechanistic considerations

Particularly interesting is the directing effect of the EWG to the final *E*/*Z* ratio of products, which is reversed between esters and nitriles. To our knowledge, this stereoselectivity trend is applied with no exceptions to all reported allylic substitutions of MBHAs.[9c,23b,26] The group of Basavaiah[9c,27] and others[26a,28] employed enolate intermediate structures to interpret the *E*/*Z* ratio switch between esters and nitriles, whereas other researchers have also followed a Michael addition/elimination theory and attributed inversion of stereochemical pattern to structural differences of the intermediate addition products.[26f,29] In addition, interpretations based on differences due to steric destabilization of either the reactants[26b,30] or pro-

ducts[26i,31] have also been proposed.[32] However, evaluation of reactivity patterns simply based on either reactant or product stability can be safe only when all compared TSs are structurally reactant-like or product-like, respectively. Another noteworthy observation is that in the case of esters, the *E*/*Z* ratio is optimized when R^1 is a phenyl group, as compared with alkyl groups, whereas in the case of nitriles this tendency is inverted. Although this tendency is not general according to the literature, relevant reaction profiles can be traced[9b–e,11,26a,b,g] with the addition of phosphites to MBHAs reported by Basavaiah perfectly matching our observations.[9c] We were unable to trace possible explanations for these preferences in the literature.

To propose a possible reason for the observed stereochemical trends, our attempt to compare TSs based on stabilization features of the products led to confusing conclusions. In particular, the higher stereoselectivity obtained for phenyl-substituted ester MBHA **6e** suggests that the difference in TS energies for *trans* and *cis* positioning of the phenyl group relative to the ester group is higher as compared with the alkyl case (e.g., **6c**), always in favor of the *trans*.[33] This implies that in the ester case, the phenyl group should exert higher steric strain in the less favored *cis*-TS as compared with alkyl groups. If we apply the same rationale in the case of nitriles, that is, the "bulkier" phenyl group prefers to be positioned at the more spacious side of the double bond that is now at the *cis* position relative to cyano group, we would expect that stereoselectivity for the phenyl-substituted nitrile MBHA **7c** would be higher as compared with the "less demanding" alkyl ones. Experimental results shown in Table 1 clearly state that this is not the case, suggesting that the initial assumption attributing product-like character for all rate-determining TSs is problematic.

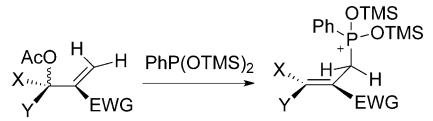
On the other hand, a mechanistic scenario that discriminates reactions between esters and nitriles according to the "lateness" of their TS could lead to more consistent conclusions. An important issue that must be taken into account concerns the conformational behavior of the phenyl group during the reaction. In particular, the phenyl group in **9e** and **14c** participates in a conjugated system, which forces a nearly coplanar conformation to be adopted that maximizes steric strain with the in-plane substituents of the double bond (Scheme 6). This could be translated to reduced rotational freedom for the C^3–C^4 of the products **9e** and **14c**, as compared with the reactants **6e** and **7c** in which C^3 is tetrahedral. Therefore, in the two conformations (*cis* and *trans*) of **6e** and **7c** that lead to different isomers, phenyl rings are more free to adjust and orientate nearly perpendicular to the C^2–C^3 bond to minimize steric interactions with the C^2 substituent (Scheme 6). Conclusively, the phenyl ring is expected to exert low steric strain at the reactants, which is gradually increased as the reaction proceeds toward the final products. The above considerations imply that for product-like TSs, the phenyl ring would behave as a "bulky" substituent, whereas for reactant-like TSs an opposite behavior is expected. In this respect, for the ester case in which product-like TSs are proposed, steric interactions between phenyl and ester groups are expected to be determining for the efficient suppression of *cis*-**9e** product, as compared with the alkyl groups in which conformational mobility may relieve excessive strain more easily. In the case of nitriles, in which reactant-like TSs are proposed, the final outcome of the reaction will depend on the *cis*/*trans* conformational ratio of **7**. For both aryl and alkyl MBHA nitriles, the substituent is better positioned closer to the smaller cyano group but this conformational equilibrium is expected to be more balanced in the case of **7c** in which the orientation of phenyl ring renders steric strain less critical.



Scheme 6. Putative interpretation of stereoselectivity profiles observed in the case of **6e** and **7c**.

Considering the proposed differences in the lateness of the rate-determining TS, we examined whether the observed stereoselectivity can be correlated with reactant energy differences in the case of nitriles and product energies in the case of esters. Quantum-mechanical DFT calculations were performed to identify the lowest-energy conformations in terms of solvent-corrected Gibbs free energy of ester MBHAs **6c** and **6e** and nitrile MBHAs **7a** and **7c** that lead to *cis* (*cis*-**6**, *cis*-**7**) and *trans* (*trans*-**6**, *trans*-**7**) isomers as well as the *cis* (*E*) and *trans* (*Z*) isomers of the primary substitution products of type **15** (that is, before Arbuzov rearrangement). As shown in Table 2, the higher energy difference between *cis*- and *trans*-**15e** (9.39 kJ mol^{-1}) as compared with the smallest energy difference between *cis*- and *trans*-**15c** (7.88 kJ mol^{-1}) correlate well with the higher *trans*-selectivity observed for the phenyl ester (*Z*/*E* 97:3) over the isobutyl analogue (*Z*/*E* 83:17 in CH_2Cl_2). This selectivity pattern is further supported by the fact that conformer *cis*-**6c** is 3.70 kJ mol^{-1} more stable than *trans*-**6c**, an order that must be reversed on route to the TS given that *trans*-stereoselectivity is finally observed. Considering that the reaction proceeds through a product-like TS, this reversal can be attainable before TS species fall into products **15c**. In the case of nitriles, the higher *cis*-stereoselectivity is observed in the case of

Table 2. Gibbs free energy differences between *cis* and *trans* conformers for reactants **6c**, **6e**, **7a** and **7c** (ΔG_r) and *cis* (*E*) and *trans* (*Z*) isomers for primary products **15c**, **15e**, **16a**, and **16c** (ΔG_p) at the B3LYP/6-311++G(3df,2p) level of theory including solvent (CH_2Cl_2) effects.



6c,**e** (EWG = CO_2Et) **15c**,**e** (EWG = CO_2Et)
7a,**c** (EWG = CN) **16a**,**c** (EWG = CN)

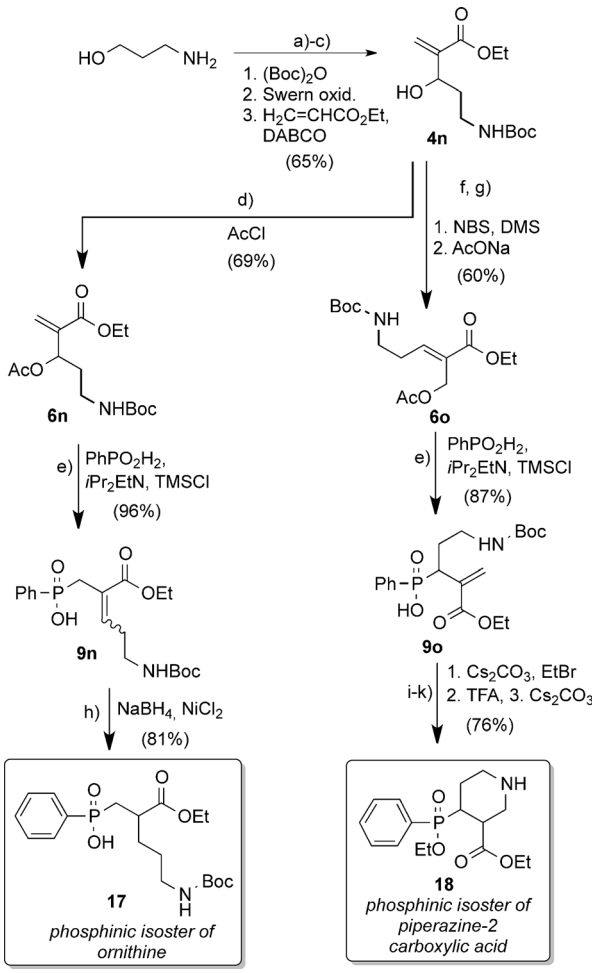
EWG	X	Y	Reactant	ΔG_r[a] [kJ mol^{-1}]	Product	ΔG_p[b] [kJ mol^{-1}]
CO_2Et	H	*i*Bu	*cis*-**6c**	−3.70	*cis*-**15c**	7.88
CO_2Et	*i*Bu	H	*trans*-**6c**		*trans*-**15c**	
CO_2Et	H	Ph	*cis*-**6e**	8.54	*cis*-**15e**	9.39
CO_2Et	Ph	H	*trans*-**6e**		*trans*-**15e**	
CN	H	*i*Bu	*cis*-**7a**	−9.54	*cis*-**16a**	−10.61
CN	*i*Bu	H	*trans*-**7a**		*trans*-**16a**	
CN	H	Ph	*cis*-**7c**	0.69	*cis*-**16c**	−16.33
CN	Ph	H	*trans*-**7c**		*trans*-**16c**	

[a] ΔG_r corresponds to the Gibbs free energy difference between lowest-energy conformations of *cis*-**6** or **7** and the corresponding *trans*-**6** or **7** ($G_{cis}-G_{trans}$). [b] ΔG_p corresponds to the Gibbs free energy difference between lowest-energy conformations of *cis*-**15** or **16** and the corresponding *trans*-**15** or **16** ($G_{cis}-G_{trans}$).

7a (*Z*/*E* 6:94) and this is in good agreement with the lowest energies of *cis* species on both reactants and products. On the other hand, the low stereoselectivity observed for the phenyl derivative **7c**, (*Z*/*E* 33:66) cannot be interpreted by examining only the energies of product **16c** isomers in which the stabilization of *trans* isomer is higher (16.33 kJ mol^{-1}) than in **16a** (10.61 kJ mol^{-1}). However, we observe that conformers of **7c** differ only by 0.69 kJ mol^{-1}. Considering a reactant-like TS character in this case, we can assume that the structural features responsible for the large stabilization of *cis*-**16c** as compared to *trans*-**16c** have not been adequately developed in the TS, which accounts for the poor experimentally observed stereoselectivity.

Applications

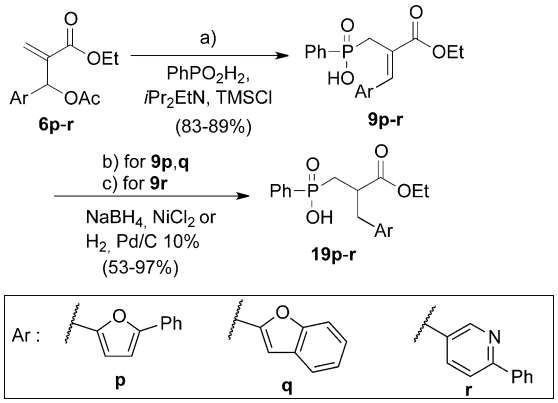
The allylic substitution reaction described herein offers many opportunities for the synthesis of phosphinopeptidic scaffolds because of 1) its higher efficiency as compared to classical protocols based on P-Michael reactions to acrylates, 2) the easier accessibility of MBHA electrophiles, 3) the possibility to deliver phosphinic scaffolds with α-substituents to phosphorus center (e.g., RXPA380, Figure 1),[4c] 4) the presence of α,β-unsaturated systems in the final products that can participate in post-diversification reactions,[10] and 5) the possibility to control stereochemistry by asymmetric hydrogenation.[9f,h,11] Moreover, starting from a single MBH allylic alcohol, different scaffolds can be approached, a feature that increases diversification possibilities. In such an example (Scheme 7), 3-aminopropanol furnishes MBHA **6n** in four high-yielding steps, which in turn can lead directly to the dehydroornithine analogue **9n**. Reduction of **9n** can be chemoselectively performed by the $NaBH_4/NiCl_2$ system, affording the phosphinic analogue of ornithine **17** in high yield (Scheme 7).[34] Furthermore, a phosphinic analogue of the unnatural amino acid piperazine-2-carboxylic acid can be synthesized starting from alcohol **4n** (Scheme 7). In particular, alcohol **4n** is converted to MBHA derivative **6o** in a two-step rearrangement process. Application of the allylic substitution affords phosphinate **9o** that can be easily transformed to **18** after suitable protection and cesium-catalyzed, intramolecular 6-*endo*-*trig* cyclization. It should be noted that the role of cesium in the last step is important to avoid lactam byproducts due to a 6-*exo*-*trig* competitive cyclization with the ethoxycarbonyl group (such byproducts were observed when DBU- or acid-catalyzed cyclization was attempted). This confor-



Scheme 7. Synthesis of ornithine (**17**) and piperazine-2-carboxylic acid (**18**) phosphinic isosters. Reagents and conditions: a) $(Boc)_2O$, THF/H_2O, 2 h, RT; b) DMSO, $(COCl)_2$, CH_2Cl_2, −45 °C, then, *i*Pr_2EtN, −30 °C, 30 min; c) H_2C=$CHCO_2Et$, DABCO, RT, 3 d, 65% for three steps; d) AcCl, pyridine, $CHCl_3$, RT, 2 h, 69%; e) $PhPO_2H_2$, *i*Pr_2EtN, **6n** or **6o**, TMSCl, CH_2Cl_2, −78 °C, then RT, 24 h for **9n**, 48 h for **9o**, then EtOH, RT, 30 min, 96% for **9n**, 87% for **9o**; f,g) 1) *N*-bromosuccinimide (NBS), dimehylsulfide (DMS), CH_2Cl_2, 2 h, RT; 2) AcONa, MeOH, 4.5 h, reflux, 60% for two steps; h) $NaBH_4$, $NiCl_2$, THF/EtOH, −30 °C, 45 min, 81%; i) Cs_2CO_3, EtBr, DMF, RT, 1.5 h; j) TFA/CH_2Cl_2, RT, 1 h; k) Cs_2CO_3, EtOH, RT, 24 h, 76% for three steps.

mationally constrained analogue (**18**) allows further diversification of the ring by projection of side chains from the secondary amine functionality.

Furthermore, the MBHA approach can easily lead to heterocycle-substituted phosphinic pseudopeptides starting from easily accessible aldehydes in four synthetic steps. We were interested in such derivatives as putative inhibitors of MMPs, encouraged by previous reports dealing with the development of isoxazole-substituted phosphinic peptides and the discovery of MMP-12 selective inhibitor **3**.[3,35] Literature reports concerning the introduction of heterocycles in the P_1' position of phosphinic pseudopeptides are limited to isoxazoles and isoxazolines,[35] therefore we applied the proposed protocol to the straightforward synthesis of three phosphinic building blocks (**9p–r**) containing diverse heterocycles (Scheme 8). Preliminary

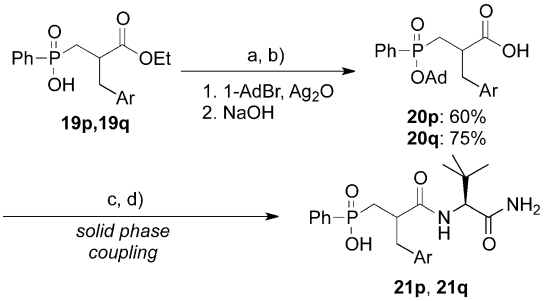


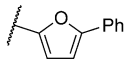
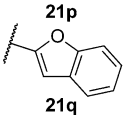
Scheme 8. Synthesis of heterocycle-substituted phosphinic isosters **19p–r**. Reagents and conditions: a) $PhPO_2H_2$, iPr_2EtN, **6**, TMSCl, MeCN, −78 °C, then RT, 6 h, 89% for **9p**, 84% for **9q**, 83% for **9r**; b) $NaBH_4$, $NiCl_2$, THF/EtOH, −30 °C, 45 min, 53% for **19p**, 69% for **19q**; c) H_2, Pd/C 10%, EtOH/H_2O, RT, 24 h, 97% for **19r** (sodium salt).

results of the inhibitory activity of phosphinic pseudotripeptides **21p,q** derived from building blocks **9p,q** against 7 MMPs demonstrate that these molecules are potent inhibitors of the target enzymes, whereas **21p** exhibits a small selectivity for MMP-12 (Scheme 9).

Conclusion

The allylic substitution reaction of MBHAs by silyl phosphonites was studied as a vehicle for the development of new, medicinally relevant phosphinic structures. The reactivity of MBHAs was found to be superior to that of acrylates as demonstrated by competition experiments and monitoring of the reaction rates by ^{31}P NMR spectroscopy. From the comparison of reaction rates recorded for MBHAs with discrete substitution patterns, an interpretation of the observed reactivity profiles and stereoselectivity trends was attempted based on the "lateness" of the rate-determining TSs. This hypothesis is supported by theoretical calculations that correlate stereochemical preferences with reactant energies in the case of nitriles and product energies in the case of esters. We believe that these mechanis-



Ar	K_i (μM) MMP-2	-3	-8	-9	-10	-12	-13
 **21p**	3.04	4.56	1.84	2.86	5.37	0.46	1.88
 **21q**	0.44	2.8	0.12	0.33	1.45	0.11	0.53

Scheme 9. Synthesis of **21p** and **21q** and inhibitory profile against MMPs. Reagents and conditions: a) 1-AdBr, Ag_2O, $CHCl_3$, reflux, 2 h; b) NaOH, EtOH/H_2O, then H_3O^+, RT, 2 h, 60% for **20p**, 75% for **20q** (2 steps); c) H-*t*BuGly-Rink, *N*,*N*′-diisopropylcarbodiimide (DIC), 1-hydroxybenzotriazole (HOBt), RT, 24 h; d) Trifluoroacetic acid (TFA)/CH_2Cl_2/triisopropylsilane (TIS)/H_2O 70:28:1:1, RT, 2 h.

tic insights may be useful to interpretations of other allylic substitution applications of related MBH derivatives. The applicability of this reaction in medicinally oriented targets was exemplified by the synthesis of functionalized, conformationally constrained, or non-classical pseudopeptidic analogues that can expand the arsenal of available phosphinic backbones in inhibitor discovery. Application of this technique in the development of potent and selective protease inhibitors is currently underway.

Experimental Section

General procedures for the synthesis of phosphinic acids of type 9 and 14 and characterization data of representative examples

Method A: A solution of $PhPO_2H_2$ (1 mmol), the corresponding MBHA **6** (or **7**) (1.15 mmol) and Hunig's base (4.0 mmol) in CH_2Cl_2 (2 mL) in a Schlenk flask was degassed by applying three freeze–pump–thaw cycles. The mixture was cooled to −78 °C and purged with Ar for 15 min. Then, the mixture was precooled at −78 °C and freshly distilled TMSCl (4.0 mmol) was added to the reaction vessel at once. The temperature was slowly raised to 25 °C and the clear solution was stirred overnight at room temperature. After the end of the reaction, the mixture was cooled to 0 °C, abs. EtOH (1 mL for 1 mmol scale) was added dropwise and the mixture was stirred at room temperature for 30 min. Removal of volatiles under vacuum afforded a viscous oil that was dissolved in 5% $NaHCO_3$. The aqueous phase was washed with hexanes (3×10 mL), acidified with HCl 1 M (×3), and the product was extracted with AcOEt (3×10 mL). The organic layer is washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Phosphinates of type **9** (or **14**) are obtained after silica gel column chromatography, using $CHCl_3$/MeOH/AcOH 7:0.1:0:1→7:0.3:0:3 as the eluent solvent system.

Method B: A solution of $PhPO_2H_2$ (1 mmol), the corresponding acetate **6** (or **7**) (1.05 mmol), and Hunig's base (4.0 mmol) in MeCN (2 mL) in a Schlenk flask was degassed by applying three freeze–pump–thaw cycles. The mixture is cooled to −78 °C and purged with Ar for 15 min. Then, the mixture was precooled at −78 °C and freshly distilled TMSCl (4.0 mmol) was added to the reaction vessel at once. The temperature was slowly raised to 25 °C and the clear solution was stirred for 6 h at room temperature. A workup was performed as in Method A.

Compound 9a: Prepared by method A. Viscous gum: TLC R_f($CHCl_3$/MeOH/AcOH 7:0.5:0.5) = 0.44; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.10 (t, J = 7.2 Hz, 3H; OCH_2CH_3), 3.03 (d, ^2J (P,H) = 18.7 Hz, 2H; PCH_2), 3.93 (q, J = 7.2 Hz, 2H; OCH_2CH_3), 5.70 (d, J = 5.2 Hz, 1H; C=CH*H*), 6.22 (dd, J = 0.7, 5.2 Hz, 1H; C=C*H*H), 7.30–7.77 ppm (m, 5H; aryl); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 33.3 (d, ^1J (P,C) = 95 Hz), 60.9, 127.9, 128.2, 129.0, 129.1, 131.1 (d, ^1J (P,C) = 135 Hz), 131.1, 131.3, 131.4, 131.6, 131.9, 132.0, 165.8, 165.8 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): δ = 40.0 ppm; IR (neat): $\tilde{\nu}$ = 2986, 1715, 1628, 1180, 1108, 961, 699 cm^{-1}; ES-MS: m/z calcd for $[C_{12}H_{15}O_4P+H]^+$: 255.1; found: 255.1; HRMS: m/z calcd for $C_{12}H_{16}O_4P$: 255.0786 $[M+H]^+$; found: 255.0788.

Compound 9b: Prepared by method B. Viscous gum: TLC R_f($CHCl_3$/MeOH/AcOH 7:0.5:0.5) = 0.35; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (t, J = 7.2 Hz, 3H; OCH_2CH_3), 1.63 (dd, J = 4.8, 7.1 Hz, 3H; C=CHCH_3), 3.00 (d, ^2J (P,H) = 18.9 Hz, 2H; PCH_2), 3.81 (q, J = 7.2 Hz, 2H; OCH_2CH_3), 6.88 (dt, J = 7.0, 14.2 Hz, 1H; C=C*H*), 7.20–7.71 ppm (m, 5H; aryl); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 14.7, 29.5 (d, ^1J (P,C) = 96 Hz), 60.4, 123.8, 124.0, 127.7, 128.0, 131.2, 131.4, 131.5 (d, ^1J (P,C) = 133 Hz), 131.7, 131.7, 141.0, 141.1, 166.3 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): δ = 40.9 (minor), 41.3 ppm; IR (neat): $\tilde{\nu}$ = 2980, 1711, 1647, 1276, 1174, 1126, 964, 733, 695 cm^{-1}; ES-MS: m/z calcd for $[C_{13}H_{17}O_4P+H]^+$: 269.1; found: 269.1; HRMS: m/z calcd for $C_{13}H_{18}O_4P$: 269.0943 $[M+H]^+$; found: 269.0938.

Compound 9e: Prepared by method B. Viscous gum: TLC R_f($CHCl_3$/MeOH/AcOH 7:0.5:0.5) = 0.64; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.1 Hz, 3H; OCH_2CH_3), 3.28 (d, ^2J (P,H) = 19.0 Hz, 2H; PCH_2), 3.96 (q, J = 7.1 Hz, 2H; OCH_2CH_3), 7.16–7.33 ppm (m, 11H; aryl, vinyl); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 30.9 (d, ^1J (P,C) = 97 Hz), 61.0, 123.7, 123.9, 127.8, 128.1, 128.3, 128.6, 129.2, 129.2, 131.2, 131.4, 131.8, 131.8, 131.9 (d, ^1J (P,C) = 133 Hz), 134.6, 134.6, 141.5, 141.7, 167.4, 167.4 ppm; ^{31}P NMR (81 MHz, CD_3OD): δ = 40.5 (minor), 41.1 ppm; IR (neat): $\tilde{\nu}$ = 3057, 2980, 1710, 1268, 1202, 1155, 964, 736, 695 cm^{-1}; ES-MS: m/z calcd for $[C_{18}H_{19}O_4P+H]^+$: 331.1; found: 331.1; HRMS: m/z calcd for $C_{18}H_{20}O_4P$: 331.1099 $[M+H]^+$; found: 331.1114.

Compound 9f: Prepared by method A. Viscous gum: TLC R_f($CHCl_3$/MeOH/AcOH 7:0.5:0.5) = 0.39; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.1 Hz, 3H; OCH_2CH_3), 1.27 (dd, J = 7.4, 16.5 Hz, 3H; $PCHCH_3$), 3.47 (dq, J = 7.3, 17.6 Hz, 1H; PC*H*), 3.96 (dq, J = 2.1, 7.1 Hz, 2H; OCH_2CH_3), 5.71 (d, J = 5.6 Hz, 1H; C=CH*H*), 6.28 ppm (d, J = 5.6 Hz, 1H; C=CH*H*), 7.24–7.75 ppm (m, 5H; aryl); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.5, 13.6, 13.9, 34.8 (d, ^1J (P,C) = 96 Hz), 60.9, 127.0, 127.2, 127.8, 128.0, 129.3, 131.8, 131.8, 131.9, 132.0, 137.8, 137.9, 166.1, 166.2 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): δ = 44.6 ppm; IR (neat): $\tilde{\nu}$ = 3056, 2980, 1717, 1438, 1262, 1141, 962, 696 cm^{-1}; ES-MS m/z: calcd for $[C_{13}H_{17}O_4P + H]^+$ 269.1; found: 269.0; HRMS: m/z calcd for $C_{13}H_{18}O_4P$: 269.0943 $[M+H]^+$; found: 269.0938.

Compound 9i: Prepared by method A. Viscous gum: TLC R_f($CHCl_3$/MeOH/AcOH 7:0.5:0.5) = 0.48; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.2 Hz, 3H; OCH_2CH_3), 4.05 (dq, J = 2.2, 7.2 Hz, 2H; OCH_2CH_3), 4.58 (d, ^2J (P,H) = 17.0 Hz, 1H; PC*H*), 6.36 (d, J = 5.5 Hz, 1H; C=CH*H*), 6.37 (d, J = 5.5 Hz, 1H; C=C*H*H), 7.05–7.74 ppm (m, 10H; aryl); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 47.4 (d, ^1J (P,C) = 96 Hz), 61.2, 127.1, 127.2, 127.8, 128.0, 128.1, 128.2, 128.4, 128.9, 129.0, 129.2, 129.8, 129.9, 129.9, 131.5, 131.7, 131.9, 132.0, 132.3, 134.2, 134.3, 135.6, 135.7, 141.8, 142.0, 165.9, 166.2 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): δ = 42.4 ppm; IR (neat): $\tilde{\nu}$ = 2980, 1712, 1438, 1237, 1127, 959, 720 cm^{-1}; ES-MS: m/z calcd for $[C_{18}H_{19}O_4P+H]^+$ 331.1; found: 331.1; HRMS: m/z calcd for $C_{18}H_{20}O_4P$: 331.1099 $[M+H]^+$; found: 331.1111.

Compound 14a: Prepared by method B. The major (*E* isomer) was isolated as a white crystalline solid after recrystallization with AcOEt. M.p. 130–133 °C; TLC R_f($CHCl_3$/MeOH/AcOH 7:0.5:0.5) = 0.44; ^{1}H NMR (200 MHz, [D_6]DMSO + 2%TFA, major isomer): δ = 0.73 (d, J = 6.6 Hz, 6H; $CH(CH_3)_2$), 1.54 (sept, J = 6.6 Hz, 1H; $CHMe_2$), 2.07 (dt, J = 3.9, 7.2 Hz, 2H; CH_2CHMe_2), 2.90 (d, ^2J (P,H) = 16.9 Hz, 2H; PCH_2), 6.20 (dt, J = 4.7, 7.7 Hz, 1H; C=C*H*), 7.40–7.85 ppm (m, 5H; aryl); ^{13}C NMR (50 MHz, [D_6]DMSO + 2%TFA, major isomer): δ = 22.0, 27.8, 27.9, 35.5 (d, ^1J (P,C) = 94 Hz), 106.3, 106.5, 117.4, 117.5, 128.4, 128.6, 131.4, 131.5, 131.6, 132.1, 134.0, 151.1, 151.3 ppm; ^{31}P NMR (81 MHz, [D_6]DMSO, mixture of isomers): δ = 31.5 (minor), 32.6 ppm; IR (KBr): $\tilde{\nu}$ = 2967, 2933, 2221, 1760, 1485, 1143, 1124, 969, 841, 753, 697 cm^{-1}; ES-MS m/z: calcd for $[C_{14}H_{18}NO_2P-H]^-$: 262.1; found: 262.2; HRMS: m/z calcd for $C_{14}H_{19}NO_2P$: 264.1153 $[M+H]^+$; found: 264.1159.

Compound 14c: Prepared by method B. The major (*E* isomer) was isolated as a white crystalline solid after recrystallization with AcOEt. M.p. 183–186 °C. TLC R_f($CHCl_3$/MeOH/AcOH 7:0.5:0.5) = 0.14; ^{1}H NMR (200 MHz, [D_6]DMSO): δ = 3.07 (d, $^2J_{PH}$ = 17.5 Hz, 2H; PCH_2), 7.06 (d, J = 4.7 Hz, 1H; C=C*H*), 7.33–7.83 ppm (m, 10H; aryl); ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 36.5, 102.6, 102.8, 118.4, 118.5, 128.2, 128.3, 128.5, 128.9, 130.2, 131.2, 131.4, 132.0, 132.0, 132.9 (d, ^1J (P,C) = 129 Hz), 133.5, 133.6, 134.2, 146.8, 147.0 ppm; ^{31}P NMR (81 MHz, [D_6]DMSO): δ = 31.5 (minor), 32.9 ppm; IR (KBr): $\tilde{\nu}$ = 3057, 3026, 2973, 2214, 1619, 1439, 1236, 1137, 970, 826, 749, 699 cm^{-1}; ES-MS m/z calcd for $[C_{16}H_{14}NO_2P-H]^-$ 282.1; found: 282.2; HRMS: m/z calcd for $C_{16}H_{15}NO_2P$: 284.0840 $[M+H]^+$; found: 284.0838.

Compound 9m: Prepared by method A. Viscous gum: TLC R_f($CHCl_3$/MeOH/AcOH 7:0.5:0.5) = 0.34; ^{1}H NMR (200 MHz, CD_3OD): δ = 2.19–2.42 (m, 2H; CH_2CH_2Ph), 2.43–2.69 (m, 2H; CH_2Ph), 2.94 (d, ^2J (P,H) = 18.2 Hz, 2H; PCH_2), 4.29–4.44 (m, 2H; $COOCH_2$), 5.85–6.10 (m, 1H; C*H*=CHPh), 6.43 (d, J = 15.6 Hz, 1H; C*H*Ph), 6.70–6.90 (m, 1H; C=C*H*), 6.93–7.70 ppm (m, 15H; aryl); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.9, 33.3 (d, ^1J (P,C) = 95 Hz), 34.3, 65.3, 123.2, 125.9, 126.5, 127.9, 128.3, 128.3, 128.5, 131.3, 131.5, 131.9, 133.6, 136.1, 140.9, 145.6, 145.8, 166.1 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): δ = 41.7 ppm; IR (neat): $\tilde{\nu}$ = 3053, 2927, 1713, 1495, 1438, 1266, 1225, 1154, 965, 735, 695 cm^{-1}; ES-MS m/z: calcd for $[C_{27}H_{27}O_4P-H]^-$ 445.2; found: 445.3; HRMS: m/z calcd for $C_{27}H_{27}NaO_4P$: 469.1544 $[M+Na]^+$; found: 469.1552.

Compound 9n: Prepared by method A. Viscous gum (Z/E = 87:13): TLC R_f($CHCl_3$/MeOH/AcOH 7:0.5:0.5) = 0.26; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.04 (t, J = 7.1 Hz; OCH_2CH_3), 1.43 (s, 9H; $(CH_3)_3C$), 2.34 (ddd, J = 4.2, 6.7, 13.8 Hz, 2H; $CHCH_2$), 3.06 (d, ^2J (P,H) = 19.0 Hz, 2H; PCH_2); 3.20 (t, J = 6.7 Hz, 2H; CH_2NH), 3.82 (q, J = 7.1 Hz, 2H; OCH_2CH_3), 6.74 (dt, J = 5.8, 7.3 Hz, 1H; C=C*H*), 7.29–7.79 ppm (m, 5H; aryl); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 28.4, 29.5, 29.9 (d, $^1J_{PC}$ = 95 Hz), 39.3, 60.8, 79.0, 124.5, 124.7, 128.0, 128.2, 131.3 (d, ^1J (P,C) = 133 Hz), 131.4, 131.6, 132.1, 132.1, 143.1, 143.3, 156.1, 166.1, 166.1 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): δ = 40.4 (minor), 40.7 ppm; IR (neat): $\tilde{\nu}$ = 2976, 1709, 1523, 1272, 1172, 1051, 962, 731, 696 cm^{-1}; ES-MS: m/z calcd for $[C_{19}H_{28}NO_6P-H]^-$ 396.2; found: 396.4; HRMS: m/z calcd for $C_{19}H_{29}NO_6P$: 398.1733 $[M+H]^+$; found: 398.1748.

Compound 9o: Prepared by method A. Viscous gum: TLC R_f($CHCl_3$/MeOH/AcOH 7:0.5:0.5) = 0.29; ^{1}H NMR (200 MHz, $CDCl_3$):

$\delta = 1.15$ (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 1.40 (s, 9H; $C(CH_3)_3$), 1.63–1.93 (m, 1H; PCHCH*H*), 1.98–2.20 (m, H; PCHC*H*H), 2.82–3.01 (m, 1H; NHCH*H*), 3.05–3.29 (m, 1H; NHC*H*H), 3.47 (ddd, $J = 3.9$, 15.9, 17.7 Hz, 1H; PC*H*), 3.98 (q, $J = 7.1$ Hz, 2H; OCH_2CH_3), 5.80 (d, $J = 5.1$ Hz, 1H ; C=CH*H*), 6.38 (d, $J = 5.6$ Hz, 1H; C=CH*H*), 7.29–7.84 ppm (m, 5H; aryl); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.0$, 28.3, 28.8, 38.1 (d, ^1J (P,C) = 97 Hz), 38.2, 38.5, 61.1, 79.2, 127.9, 128.2, 129.1, 131.4, 131.6, 131.7, 131.8, 132.0, 132.1, 132.1, 135.4, 135.5, 155.8, 166.3, 166.4 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 43.4$ ppm; IR (neat): $\tilde{\nu} = 2979$, 1714, 1517, 1251, 1172, 958 cm^{-1}; ES-MS: *m/z* calcd for $[C_{19}H_{28}NO_6P-H]^-$: 396.2; found: 396.3; HRMS: *m/z* calcd for $C_{19}H_{29}NO_6P$: 398.1733 $[M+H]^+$; found: 398.1727.

Compound 9p: Prepared by method A. Viscous gum: TLC R_f($CHCl_3$/MeOH/AcOH 7:0.5:0.5) = 0.46; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.18$ (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 3.64 (d, ^2J (P,H) = 19.8 Hz, 2H; PCH_2), 4.05 (q, $J = 7.1$ Hz, 2H; OCH_2CH_3), 6.50–6.70 (m, 2H; furyl), 7.04–7.75 ppm (m, 11H, C=C*H*; aryl); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 14.0, 31.7 (d, $^1J_{PC} = 95$ Hz), 60.9, 107.2, 118.4, 118.6, 118.6, 124.2, 127.0, 127.2, 127.4, 127.7, 128.0, 128.6, 129.6, 130.3, 131.1, 131.3, 131.4, 131.5, 132.9, 150.0, 150.1, 155.7, 155.7, 167.2, 167.2 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 40.2$ (minor), 41.7 ppm; IR (neat): $\tilde{\nu} =$ 2926, 1730, 1438, 1173, 965, 761, 694 cm^{-1}. ES-MS: *m/z* calcd for $[C_{22}H_{21}O_5P-H]^-$: 395.4; found: 395.2; HRMS: *m/z* calcd for $C_{22}H_{22}O_4P$: 397.1205 $[M+H]^+$; found: 397.1213.

Computational methods

DFT calculations were carried out with the Gaussian 03 Rev.01 package.[36] Reactants, products and transition states were fully optimized in the absence of solvent and their vibrational frequencies were calculated at the B3LYP/6–31G(d′) level of theory.[37] A systematic conformational search was performed for all species and the structures with the lowest solvent-corrected Gibbs Free Energies were considered. Transition states were obtained by relaxed potential surface scans followed by a first-order saddle point optimization using the Berny algorithm.[38] Stationary points obtained were verified to be true minima for reactants and products and first-order saddle points for transition states by examination of vibrational frequencies and corresponding atomic motions in the case of TSs. Electronic energies were refined by single-point calculations at the B3LYP/6–311++G(3df,2p) level of theory with solvent effects (CH_2Cl_2, $\varepsilon = 8.93$) taken into account using the Integral Equation Formalism of the Polarizable Continuum Model (IEF-PCM).[39] Gibbs free energies at 298.15 K were calculated by assuming the rigid-rotor and harmonic oscillator approximations.

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