ChemPubSoc Europe

DOI: 10.1002/chem.201503403

CHEMISTRY A European Journal Full Paper

Natural Products

Gold- or Silver-Catalyzed Syntheses of Pyrones and Pyridine Derivatives: Mechanistic and Synthetic Aspects

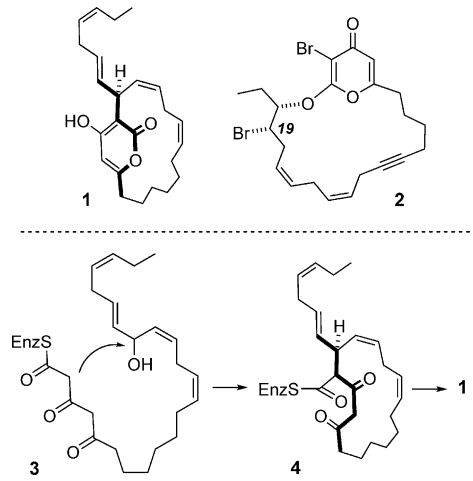
Johannes Preindl, Kévin Jouvin, Daniel Laurich, Günter Seidel, and Alois Fürstner*[a]

Abstract: 3-Oxo-5-alkynoic acid esters, on treatment with a carbophilic catalyst, undergo 6-*endo-dig* cyclization reactions to furnish either 2-pyrones or 4-pyrones in high yields. The regiochemical course can be dialed in by the proper choice of the alcohol part of the ester and the π-acid. This transformation is compatible with a variety of acid-sensitive groups as witnessed by a number of exigent applications to the total synthesis of natural products, including pseudopyronine A, hispidine, phellinin A, the radininol family, neurymenolide, violapyrone, wailupemycin and an unnamed brominated 4-pyrone of marine origin. Although the reaction proceeds well in neutral medium, the rate is largely increased when HOAc is used as solvent or co-solvent, which is thought to favor the protodeauration of the reactive alkenyl-gold intermediates as the likely rate-determining step of the catalytic cycle. Such intermediates are prone to undergo diauration as an off-cycle event that sequesters the catalyst; this notion is consistent with literature data and supported by the isolation of the *gem*-diaurated complexes **12** and **15**. Furthermore, silver catalysis allowed access to be gained to 2-alkoxypyridine and 2-alkoxyisoquinoline derivatives starting from readily available imidate precursors.

Introduction

During the total synthesis of the structurally fairly unique marine natural products neurymenolide A (**1**) and its unnamed sibling **2** we faced the need to develop novel approaches to 2-pyrones and 4-pyrones, respectively (Scheme 1).[1–3] The skipped unsaturations in the aliphatic tethers of these *ansa*-compounds are exceptionally isomerization-prone; in case of compound **2**, the challenge is further increased by the presence of a homoallylic bromine substituent at C19 with latent "non-classical" carbocation reactivity, as well as by the fragile ketene-acetal motif that links the heterocyclic core to the aliphatic chain.

In biosynthetic terms, both secondary metabolites are thought to derive from 1,3,5-tricarbonyl precursors such as **3** formed by chain-extension of a polyunsaturated fatty acid, which then cyclize to the respective pyrone rings.[4,5] Early attempts at emulating this reactivity mode in the laboratory suggested that the required conditions are too harsh to qualify for a key step of a projected total synthesis of these exigent targets.[6,7] It was therefore mandatory to develop a much milder entry; this new approach must also be regioselective, such that either a 2-pyrone or a 4-pyrone unit can be accessed with high fidelity.[8,9] As will be outlined below in some detail, a noble-metal catalyzed cyclization reaction shows the required profile; it does not only provide access to substituted pyrones that are difficult to make otherwise, but can also be extended to the preparation of various N-heterocycles.



Scheme 1. Top: Cyclophanic pyrone derivatives of algal origin (in case of **2**, only the relative configuration is known); bottom: putative biosynthetic pathway to neurymenolide A (**1**).

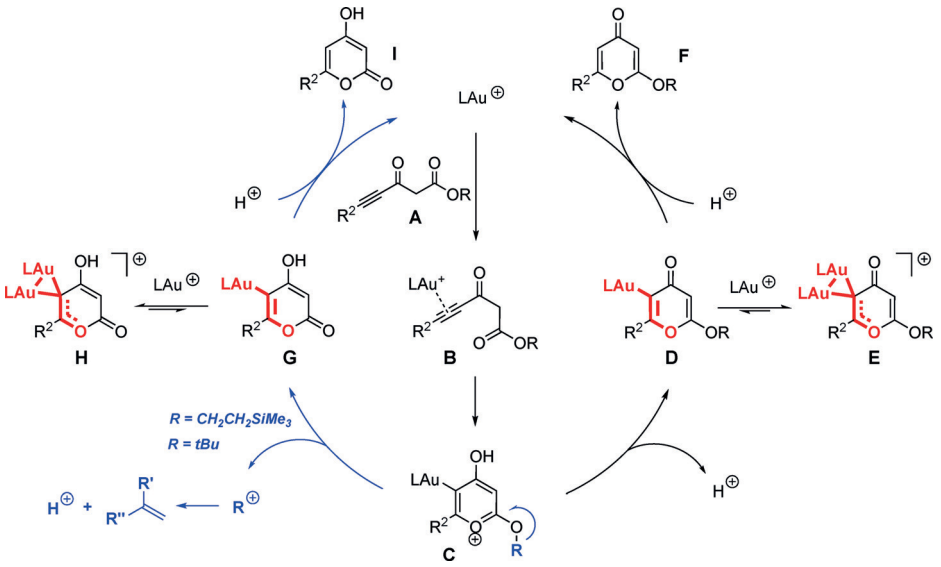
Results and Discussion

Concept

The activation of π-bonds by carbophilic catalysts, most notably those based on platinum or gold, provides an opportunity for the manipulation of functional groups in a way that is largely orthogonal to established carbonyl chemistry.[10,11] Since an internal alkyne can be seen as a ketone surrogate, we conceived that a substrate of the general type **A** is synthetically

[a] J. Preindl, Dr. K. Jouvin, D. Laurich, Ing. G. Seidel, Prof. A. Fürstner
Max-Planck-Institut für Kohlenforschung
45470 Mülheim/Ruhr (Germany)
E-mail: fuerstner@kofo.mpg.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201503403.



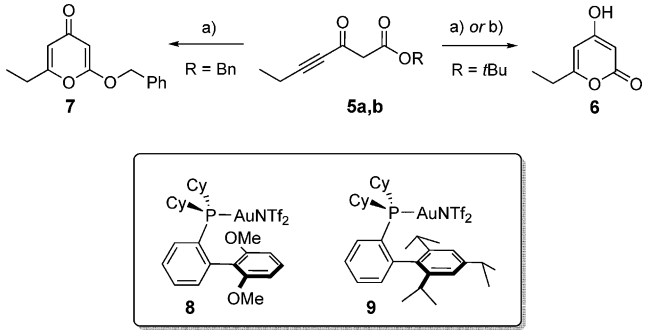
Scheme 2. Bifurcated pathway that allows 2-alkoxy-4-pyrones (**F**) and 4-hydroxy-2-pyrones (**I**) to be formed with high selectivity, depending on the nature of the ester terminus R in the substrate **A** and/or the chosen carbophilic catalyst; *gem*-diaurations as conceivable off-cycle events.

equivalent to tricarbonyl compounds such as **3** commonly employed in (biomimetic) cyclization reactions of the type referred to above.

Such substrates might lend themselves to regioselective pyrone formation,[12] provided the adjacent ester group attacks the activated triple bond in a 6-*endo*-*dig* fashion (Scheme 2): if the resulting intermediate **C** simply releases a proton, a 2-alkoxy-4-pyrone **F** will ensue upon protodemetallation of **D**. Alternatively, **C** might be engineered for rapid loss of a (stabilized) cation [R^+] with formation of an intermediate of type **G**, which would redirect the pathway to the corresponding 4-hydroxy-2-pyrone **I**. It is expected that an increased electrophilicity of the catalyst facilitates the breakdown **C** → **G**. Hence, access to either pyrone series might be gained from a single type of substrate upon proper choice of the ester group R and/or the π-acidic catalyst.

The model substrates **5a**,**b** differing only in their ester terminus served to test this concept (Scheme 3).[1,13] In line with our expectations, treatment of **5a** (R = *t*Bu) with catalytic amounts of various complexes of the type LAuCl, after in situ or ex situ ionization with $AgNTf_2$,[14] resulted in the clean and essentially quantitative formation of product **6** as judged by NMR. The cleavage of the *tert*-butyl group off the putative intermediate of type **C** (R = *t*Bu) is obviously fast enough to funnel this species exclusively to the desired 2-pyrone product; subsequent release of a proton with concomitant formation of isobutene ensures catalyst turnover. Importantly, substrate **5b** (R = Bn) bearing a benzyl rather than a *tert*-butyl ester furnished the regioisomeric 4-pyrone **7** under otherwise identical conditions.[1]

Best results were obtained with Buchwald-type (dialkyl)biaryl phosphines as ancillary ligands L.[15] Moreover, the chosen solvent was found to exert a strong influence: clean but slow reactions were observed in CH_2Cl_2, $CHCl_3$, 2-dichloroethane, toluene, Et_2O, MeCN, and nitromethane, whereas the use of THF led to product mixtures. By far the fastest rates were obtained

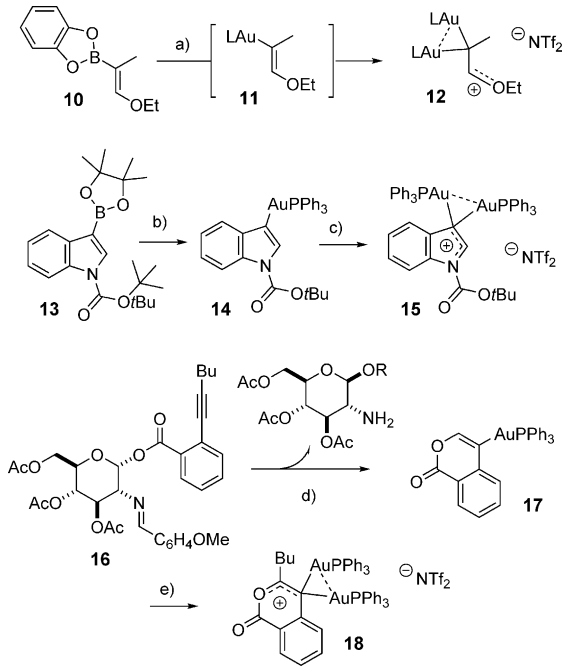


Scheme 3. Model reactions: the choice of the ester terminus determines the regioselective course of gold catalyzed pyrone formation. a) [(SPhos)$AuNTf_2$] (**8**) (1 mol%), HOAc, 94% (**6**), 94% (**7**); b) [(XPhos)$AuNTf_2$] (**9**) (1 mol%), HOAc, 92% (**6**).

when HOAc was used as the reaction medium or as cosolvent to MeCN or nitromethane.[1] Under these conditions, the reaction proceeded within minutes and the catalyst loading could be reduced to ≤1 mol% without noticeable loss in efficiency. Several control experiments proved that neither the Brønsted acid itself nor any residual $AgNTf_2$ are accountable for the pyrone formation: even after 14 d less than 20% of product **6** had formed in the absence of the gold catalyst, whereas $AgNTf_2$ (10 mol%) in HOAc or nitromethane required ≈ 24 h reaction time for full conversion. Moreover, addition of $HNTf_2$ (5 mol%) to a solution of **5a** in HOAc resulted only in the cleavage of the *tert*-butyl ester; no pyrone was observed in this case by NMR, thus excluding that $HNTf_2$ formed in situ by protonation of the counterion by HOAc is the actual catalytically competent species.[16]

Mechanistic Implications

The remarkable co-catalytic effect of HOAc deserves further comment. Previous investigations in our laboratory had revealed that the functionalized alkenylgold complex **11** (prepared from **10** by gold-for-boron exchange) reacts instantaneously with a second $[Ph_3PAu]^+$ fragment to form the *gem*-diaurated species **12a**, which turned out to be surprisingly stable and unreactive (Scheme 4).[17,18] This bias is thought to reflect the affinity of the transient alkenyl gold species **11** for the "soft" and polarizable late-transition metal cation, which is (much) higher than the affinity for the "hard" proton and therefore becomes competitive. As the proposed organogold intermediates **D** and **G** passed through en route to a pyrone feature a similar β-oxygenation pattern,[19] they might be similarly susceptible to *gem*-diauration with formation of off-cycle intermediates of type **E** and **H**, respectively, that sequester the catalyst in an unreactive form (Scheme 2).[1] Under this proviso, it seems likely that protodeauration represents the rate-determining step of the catalytic cycle,[20] which in turn nicely explains why an acidic medium instigates a significant rate acceleration.[21,22]



Scheme 4. a) $[(L)AuNTf_2]$, Cs_2CO_3, THF, 85% (**12a**, L = PPh_3), 87% (**12b**, L = XPhos), 73% (**12c**, L = SIPr); b) $[(Ph_3P)AuNTf_2]$, Cs_2CO_3, THF, 80%; c) $[(Ph_3P)AuNTf_2]$, CH_2Cl_2, 93%; d) $[(Ph_3P)AuOTf]$, 4-penten-1-ol, toluene, 91%, cf. ref. [23]; e) $[(Ph_3P)AuNTf_2]$, $CDCl_3$, quant., cf. ref. [27]; SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidin2-ylidene.

One might object that this interpretation is based on the *gem*-diorganogold species **12a** (L = PPh_3) comprising Ph_3P ligands,[17] whereas pyrone formation is best achieved with gold catalysts endowed with SPhos or XPhos, the sheer size of which might impede or even suppress an analogous pathway. A control experiment, however, proved that *gem*-diauration of **10** proceeded readily even with the most bulky complex $[(XPhos)AuNTf_2]$; the analogous gold source $[(SIPr)AuNTf_2]$ comprising yet another sterically demanding ligand of a different shape also reacted without incident (Scheme 4). The structures of the resulting *gem*-diaurated products **12b** and **12c** in the solid state show that the long bond lengths entertained by the gold centers alleviate the crowding (Figures 1 and 2).

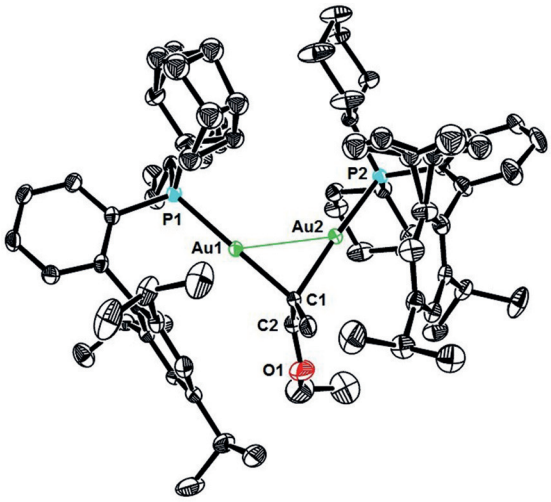


Figure 1. Structure of complex **12b** (L = XPhos) in the solid state; only the complex cation is depicted, whereas the escorting $[NTf_2]^-$ anion as well as co-crystallized CH_2Cl_2 are omitted for clarity. Selected bond lengths [Å]: C1–Au1 2.140(4), C1–Au2 2.117(4), C1–C2 1.390(7), C2–O1 1.321(5), Au1–Au2 2.816(4).

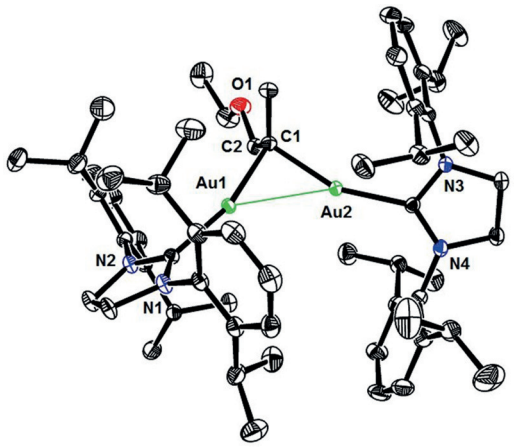


Figure 2. Structure of complex **12c** (L = SIPr) in the solid state; only the complex cation is depicted, whereas the escorting $[NTf_2]^-$ anion as well as co-crystallized CH_2Cl_2 are omitted for clarity. Selected bond lengths [Å]: C1–Au1 2.109(3), C1–Au2 2.122(3), C1–C2 1.358(5), C2–O1 1.348(4), Au1–Au2 2.829(4).

Therefore it seems highly unlikely that *gem*-diauration can be precluded solely by choosing bulky ancillary ligands. Similar conclusions were reached by other authors for different model compounds.[24] Complexes **12b,c** feature structural characteristics similar to those observed for the parent complex **12a**.[17]

Most notable is the fact that the former C=C bond has lost much of its double bond character, whereas the C–O bond is significantly contracted, indicative of build-up of positive charge density at this site. In the extreme, these complexes can be thought of as consisting of an oxocarbenium motif stabilized via hyperconjugation by a flanking dimetalated center.[25] An aurophilic interaction further supports the particular assembly mode of these unusual complexes.[26]

While complexes **12a–c** invariably comprise an alkoxide substituent at the β-position, the proposed intermediates **D** and **G** feature a (vinylogous) β-acyloxy moiety (see Scheme 2). Though clearly less electron releasing, even such a motif provides sufficient activation for diauration to proceed. Thus, Yu and co-workers managed to isolate the *gem*-diaurated coumarin intermediate **18** formed upon treatment of the glucosyl alkynylbenzoate with $[Ph_3PAu]^+$ (Scheme 4).[27] Along similar lines, we found that the enamide substructure of an indole is amenable to *gem*-diauration, a fact that is relevant for the discussion of the N-heterocycle formations outlined below. In this case, the mono-aurated species **14** can be formed as a discrete species, which reacts further on exposure to an extra equivalent of $[(Ph_3P)AuNTf_2]$. The contracted N1–C1 bond (1.378(3) Å) in **15** indicates considerable N-acyliminium character inherent to this remarkable diaurated complex (Figure 3).[25,28] In any case, the examples shown in Scheme 4 collectively support the notion that (moderately) electron rich π-systems are highly prone to diauration. This bias likely represents a serious competition for productive catalyst turnover and has to be taken into consideration in any of the noble-metal catalyzed heterocycle syntheses discussed herein.

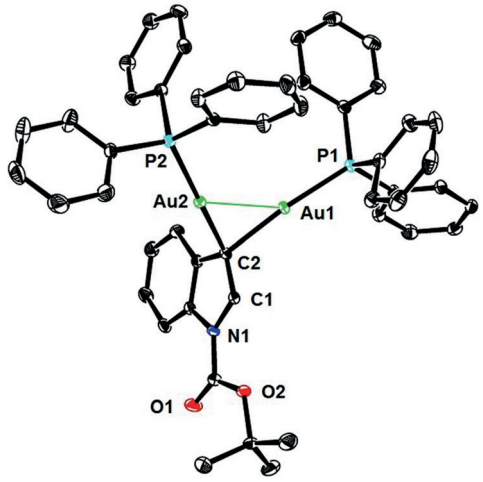


Figure 3. Structure of complex **15** in the solid state; only the complex cation is depicted for clarity. Selected bond lengths [Å]: N1–C1 1.378(3), C1–C2 1.387(3), C2–Au1 2.117(2), C2–Au2 2.127(2), Au1–P1 2.270(8), Au2–P2 2.261(7), Au1–Au2 2.764(4).

4-Hydroxy-2-pyrones

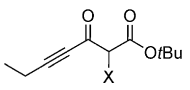
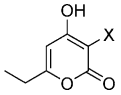
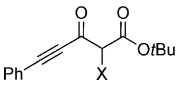
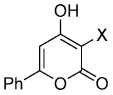
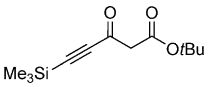
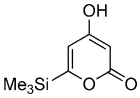
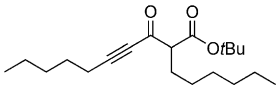
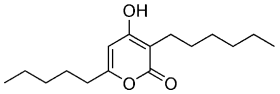
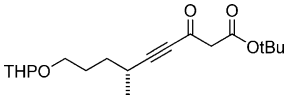
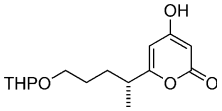
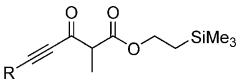
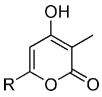
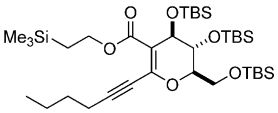
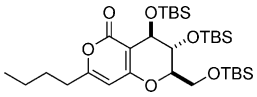
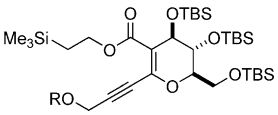
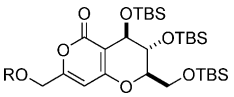
Entries 1–8 in Table 1 show an assortment of 4-hydroxy-2-pyrones formed by gold-catalyzed cyclization of the corresponding β-keto esters comprising a *tert*-butyl ester terminus, which in turn were readily prepared by Claisen condensation (see the Supporting Information). The reactions proceeded cleanly, scaled well and tolerated various substituents. Even halogenated substrates were cyclized without incident (entries 3, 5), whereas a C-silylated alkyne furnished the desired 2-pyrone in only modest yield (entry 6); this result echoes previous experiences of our group with substrates of this sort.[29] The product shown in entry 7 is the antibiotic pseudopyronine A, an inhibitor of microbial fatty acid biosynthesis,[30] whereas entry 8 features a building block for the total synthesis of the mycopyronins and related RNA-polymerase inhibiting antibiotics.[31,32]

tert-Butyl ester derivatives are not the only substrates amenable to 4-hydroxy-2-pyrones formation; trimethylsilylethyl 3-oxoalkanoates are equally suitable and have the additional bonus of being easy to make by conventional esterification (entries 9–13). By virtue of the β-cation-stabilizing effect of the silyl group,[33] a putative intermediate of type **C** (R = $CH_2CH_2SiMe_3$) collapses in a fashion analogous to that for R = *t*Bu. This variant also allowed a set of products to be formed in which the pyrone ring is annulated to a glucose moiety; for the sake of the acid labile silyl ether protecting groups, these particular cyclization reactions were performed in nitromethane rather than HOAc. The success of these model studies paved the way for an application to the radicinol series (see below).

2-Alkoxy-4-pyrones

The ready formation of the 2-benzyloxy-4-pyrone **7** from the model compound **5b** (R = Bn) under otherwise identical conditions suggested that the course of the reaction is largely determined by the very nature of the ester terminus in the starting material (Scheme 3). Thus, substrates derived from a primary or secondary alcohol component lead to intermediates of type **C** that evolve via simple proton loss to the corresponding 2-alkoxy-4-pyrones **F**. The examples shown in Table 2 (entries 1–5) prove that this reactivity pattern is general; some of the products served as model compounds for the total synthesis of the algal metabolite **2** mentioned in the Introduction. The very mild conditions of this new method transpire from the successful formation of the pyrones shown in entries 4 and 5 which contain a protected alcohol substituent at a homoallylic site in the tether; release of the masked "non-classical" cation would obviously be detrimental. Moreover, the presence of double bonds in the cyclization precursor does not obstruct the necessary activation of the alkyne unit by the π-acidic catalyst, although coordination of gold to an alkene is thermodynamically perhaps even more favorable.[11] Equally noteworthy is the successful cyclization of a substrate containing more than one acetylene unit (entry 5): although the triple bond conjugated to the carbonyl group is actually the least electron rich and hence the least affine to the carbophilic gold catalyst, it is the only site featuring a nucleophile at an appropriate distance and hence provides a productive outlet. The selective formation of the polyunsaturated products shown in entries 4 and 5 is therefore thought to reflect kinetic control, which in

Table 1. Gold-catalyzed preparation of 4-hydroxy-2-pyrones.[a]

Entry	Substrate	Product	Yield [%]
1			94 (X = H)
2			97 (X = Me)
3			82 (X = Br)
4			99 (X = H)
5			85 (X = F)
6			45
7			96
8			83
9			97 (R = Me)[b]
10			94 (R = Ph)[b]
11			83[b,c]
12			89 (R = H)[b,c]
13			91 (R = Ac)[b,c]

[a] Unless stated otherwise, all reactions were carried out with [(SPhos)AuNTf$_2$] (5 mol%) as the catalyst in HOAc as the solvent. [b] Using only 1 mol% of the catalyst. [c] In nitromethane; TBS = *tert*-butyldimethylsilyl; THP = tetrahydropyranyl.

turn implies that gold-alkyne π-complex formation is fast and reversible.[34,35]

Interestingly, even substrates of type **A** containing a *tert*-butyl ester terminus can be converted into the corresponding 4-pyrones, provided that the gold catalyst is replaced by the less electrophilic silver salt AgNTf$_2$ in the presence of *N*,*N*′-dimethylethylenediamine (DMEDA) as a proton scavenger (entries 6–8). We therefore conclude that the approach described herein constitutes the arguably most general entry into the 2-alkoxy-4-pyrone series known to date.[9] Its successful implementation into the total synthesis of the exceptionally taxing marine natural product **2** highlights its preparative significance.[2]

Applications to Natural Product Synthesis: Hispidine and Phellinin A

The ability to engage polyunsaturated precursors in cyclization opened an expedient entry into styrylpyrones such as phellinin A (**26**), an annulated pyrone derivative with considerable radical scavenging capacity that exists in nature as two equilibrating diastereomers.[36,37] To this end, commercial **19** was subjected to a high yielding Hundsdieker reaction to afford the corresponding alkenyl bromide **20**,[38] which was then cross coupled with ethyl propiolate[39] to give ester **21** amenable to a Claisen condensation with lithio *tert*-butyl acetate (Scheme 5). The resulting β-ketoester **22**, when treated with catalytic amounts of **8** in HOAc, furnished the desired 2-pyrone **23**, which is hardly soluble in the medium; for its isolation, it only has to be rinsed and dried. Cleavage of the ketal with BCl_3 as described in the literature affords hispidine **24**,[40] which is the historically first 2-pyrone to be isolated from natural sources.[37,41]

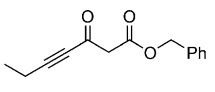
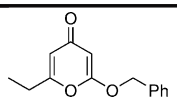
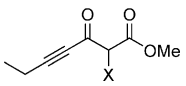
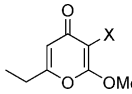
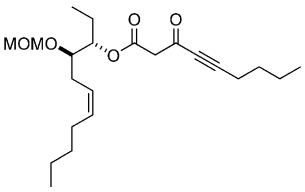
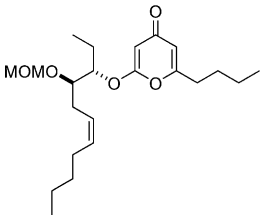
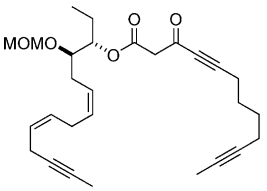
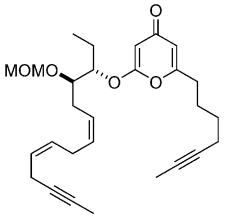
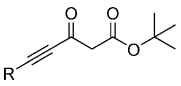
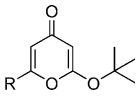
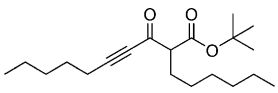
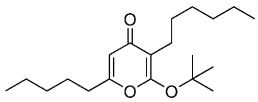
A formal [3+3] cycloaddition[42] between **23** and enal **29** gave the annulated product **25** in good yield, provided that strictly anhydrous conditions were secured. Final acetal cleavage released phellinin A (**26**) as a yellow/orange powder that is only sparingly soluble in MeOD or CD_2Cl_2; it consists of a mixture of diastereomers which equilibrate in solution and therefore cannot be separated.[36] The required enal partner **29** was prepared in a few straightforward steps from Romascone (**27**). The key step is the V(O)(OSiPh$_3$)$_3$ catalyzed Meyer-Schuster rearrangement of propargyl alcohol **28** to form the targeted enal **29** in good overall yield.[43,44]

The Radicinol Family

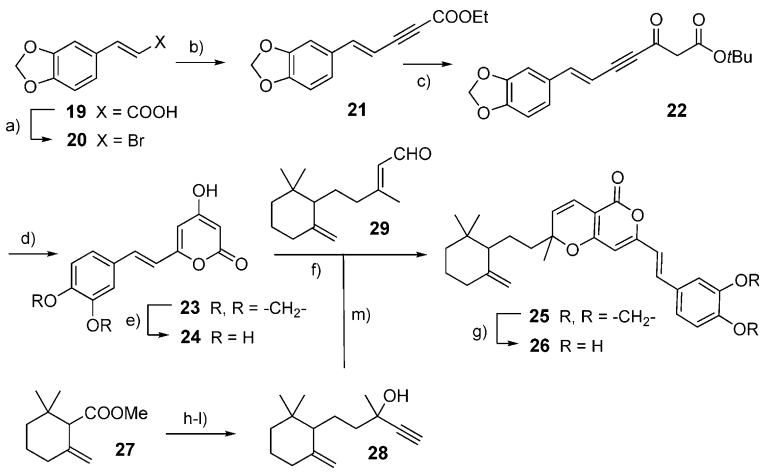
Plant pathogens are a prolific source of possible herbicidal lead structures. In this context, the radicinol family of bicyclic 2-pyrone derivatives deserves mentioning, which derives from different phytopathogenic fungi of the *Stemphylium*, *Cochliobus*, *Bipolaris*, *Phoma* and *Alternaria* genera (Figure 4).[45] The composition of the crude extracts depends not only on the particular strain but is also strongly affected by the natural substrate (or culture medium) on which they grow. Interestingly, the different fungal strains seem capable of permutating the configurations and, in part, the oxidation level at the C3 and C4 positions, whereas C5 remains invariably (*S*)-configured. Since the phytotoxic activity of the individual family members is strongly correlated with the stereostructure,[45] it is of considerable interest to extend the screening to the missing isomers comprising a non-natural (5*R*)-center.

Commercial phenylthio β-D-glucopyranoside (**33**) served as a convenient point of departure (Scheme 6). Selective tosylation of the primary position, benzylation of the remaining hydroxyl groups, reduction of the sulfonate ester with LiAlH$_4$[46] and S-oxidation with *m*CPBA gave product **35** as a mixture of the diastereomeric sulfoxides. Treatment with two equivalents of LDA at low temperature furnished the corresponding lithiated glycal derivative **36**,[47] which was quenched with trimethylsilylethyl chloroformate to give ester **37** in excellent yield. This

Table 2. π-Acid-catalyzed preparation of 2-alkoxy-4-pyrones.[a]

Entry	Catalyst	Substrate	Product	Yield [%]
1	**8**[b]			94
2	**8**[b]			89 (X = H)
3	**8**			66 (X = Br)
4	**8**			95[c]
5	**8**			86[c]
6	$AgNTf_2$[d]			85 (R = C_6H_{13})
7	$AgNTf_2$[d]			87 (R = Ph)
8	$AgNTf_2$[d]			88

[a] Unless stated otherwise, all reactions were carried out with a catalyst loading of 5 mol% in HOAc as the solvent. [b] With 1 mol% of catalyst. [c] MeCN/HOAc (5:1). [d] With AgOTs and DMEDA (5–7.5 mol% each) in $CHCl_3$ as the solvent; DMEDA = *N*,*N*′-dimethylethylenediamine; MOM = Methyloxymethyl.



Scheme 5. Preparation of hispidine (**24**) and phellinine A (**26**): a) NBS, Et_3N (5 mol%), $MeCN/H_2O$ (9:1), 91%; b) (i) ethyl propiolate, LDA, THF, −78 °C; (ii) $ZnBr_2$, $[(Ph_3P)_4Pd]$ (5 mol%), −78 °C→RT, 68%; c) *tert*-butyl acetate, LDA, THF, −78 °C, then **21**, 89%; d) **8** (2 mol%), HOAc, 90%; e) BCl_3, CH_2Cl_2, −20 °C→RT, 63%; f) Ac_2O, piperidine, EtOAc, 85 °C, 82%; g) BCl_3, CH_2Cl_2, 50 °C, 36%; h) $LiAlH_4$, THF, 0 °C→RT, 90%; i) DMSO, oxalyl chloride, CH_2Cl_2, −78 °C, then Et_3N, −78 °C→RT; j) $Ph_3P{=}CHC(O)Me$, toluene, reflux, 67% (over both steps); k) $[(Ph_3P)_2PdCl_2]$ (5 mol%), Bu_3SnH, NH_4Cl, aq. THF, 76%; l) HC≡CMgBr, THF, 0 °C→RT, 95%; m) $[V(O)(OSiPh_3)_3]$ (5 mol%), Ph_3SiOH (3 mol%), toluene, 120 °C (microwave), 81%; LDA = lithium diisopropylamide; NBS = *N*-bromosuccinimide.

compound underwent a 1,4-addition/elimination process[48] on treatment with lithio pent-1-yn-3-ene generated in situ from the *gem*-dibromide **38**[49] and BuLi; gratifyingly, both diastereomeric sulfoxides reacted similarly well, thus making a separation unnecessary.

In line with our expectation, compound **39** was readily transformed into pyrone **40** on exposure to catalytic amounts of complex **8** in nitromethane; subsequent deprotection with BCl_3 gave *ent*-**27**. Interestingly, when the cyclization reaction was performed in HOAc, pyrone formation was accompanied by a selective replacement of the BnO-group at C3 by an acetate moiety to give **42a** (R = Ac) as an 8.2:1 mixture of diastereomers, which were readily separable by flash chromatography. Careful analysis of the NOE contacts and the ^3J coupling constants proved that inversion is the dominant stereochemical course; yet, it is likely that a cationic intermediate of type **41** is operative under the acidic conditions, which gains stabilization by orbital overlap with the adjacent pyrone ring and the vinylogous ether oxygen substituent; the incoming acetate nucleophile approaches this species preferentially *trans* to the benzyl ether substituent for stereoelectronic reasons.[50] In any case, global deprotection of the major isomer **42a** afforded *ent*-**29** in high overall yield.

The remarkable ease and selectivity of this substitution reaction suggested that direct access to 3-methoxy-3-*epi*-radicinol (*ent*-**32**) might also be gained if one engages MeOH instead of HOAc as external nucleophile. In fact, treatment of **39** with complex **8** (1 mol%) in MeOH in the presence of dilute HCl gave pyrone **42b** (R = Me) with a single methyl ether in place (d.r. 2.8:1). Debenzylation of the major isomer furnished *ent*-**32**, the constitution and stereostructure of which are unambiguous. Because the data of the synthetic material, however, deviate from those of the natural product reported in the literature (for a comparison, see the Supporting Information), questions remain as to whether the structure of this particular natural product has been properly assigned by the isolation team.[45c]

As outlined above, this study deliberately sought access to the non-natural (5*R*)-series. Yet, we like to emphasize that the proper natural products could be obtained analogously by starting from cheap L-rhamnose instead of D-glucose.

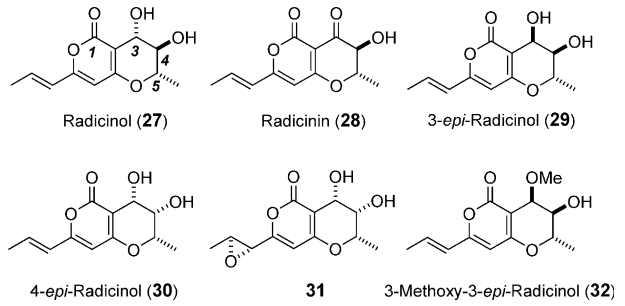
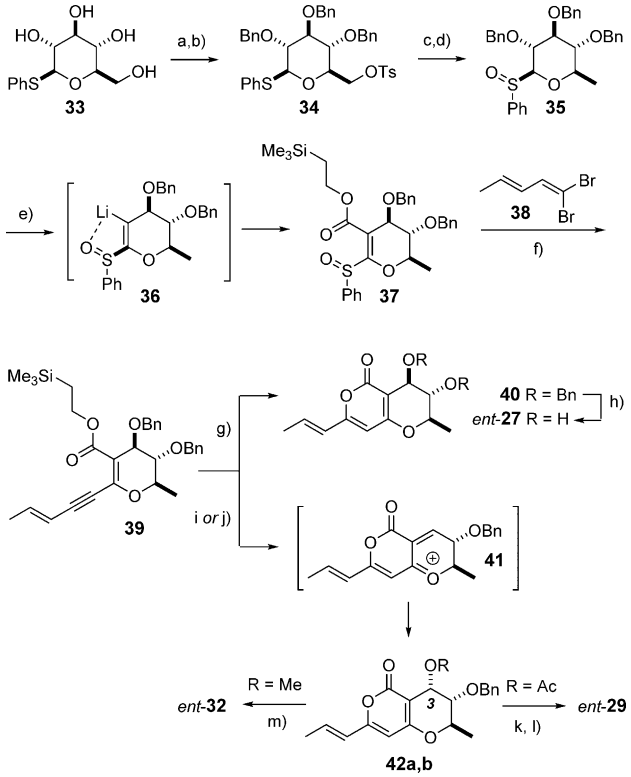
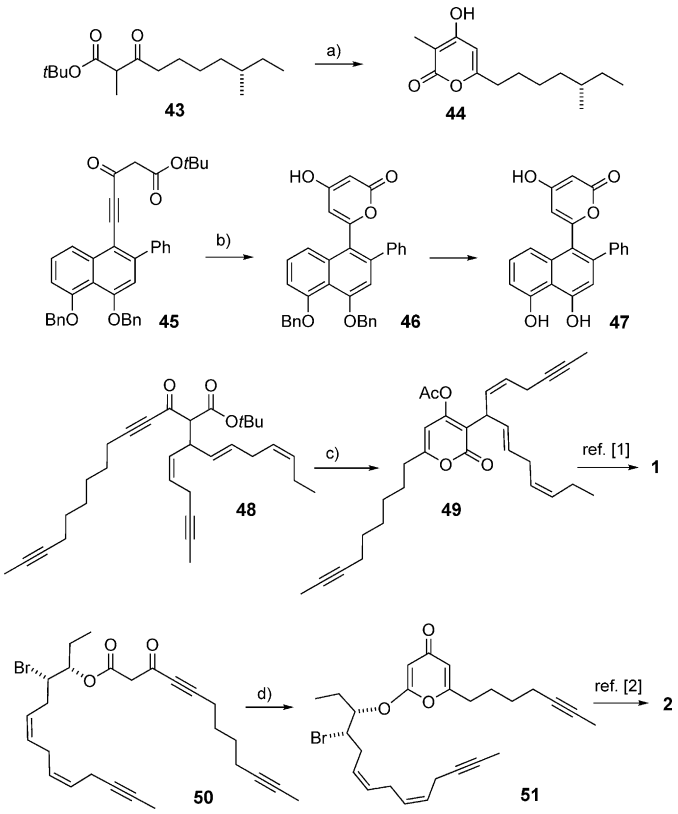


Figure 4. Naturally occurring members of the radicinol family.



Scheme 6. a) TsCl, pyridine, 0 °C, 68%; b) NaH, BnBr, DMF, 0 °C→RT, 87%; c) $LiAlH_4$, Et_2O, reflux, 89%; d) *m*CPBA, CH_2Cl_2, 0 °C, 94% (d.r. 1.8:1); e) (i) LDA, THF, −78 °C; (ii) $Me_3SiCH_2CH_2C(O)Cl$, HMPA, 96-99%; f) (i) **38**, *n*BuLi, THF, −78 °C→0 °C; (ii) **37**, −78 °C → −55 °C, 82-85%; g) **8** (1 mol%), $MeNO_2$, 94%; h) BCl_3, CH_2Cl_2, −78 °C, 88%; i) **8** (1 mol%), HOAc, 82% (R = Ac, d.r. 8.2:1); j) **8** (1 mol%), MeOH, HCl, 91% (R = Me, d.r. 2.8:1); k) K_2CO_3, aq. MeOH, 90%; l) BCl_3, CH_2Cl_2, −78 °C, 91%; m) BCl_3, CH_2Cl_2, −78 °C, 72%.



Scheme 7. a) $[(Ph_3P)AuNTf_2]$ (10 mol%), $MeNO_2$/HOAc (4:1), 81%; b) **9** (5 mol%), $MeNO_2$, 78%; c) (i) **9** (5 mol%), $MeNO_2$/HOAc (4:1); (ii) Ac_2O, Et_3N, CH_2Cl_2, 0 °C, 73% (over both steps); d) **8** (3 mol%), MeCN/HOAc (4:1), 97%.

Examples from the Literature

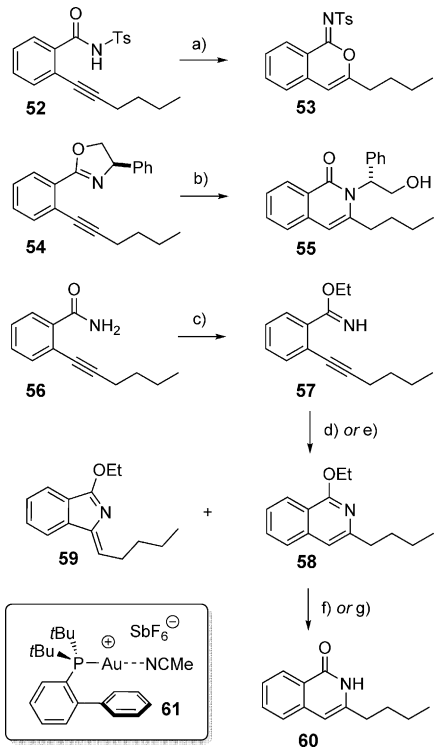
In addition to the case studies outlined above, a number of recent reports in the literature highlight the broad scope of our new pyrone synthesis. Specifically, the final step en route to the cytotoxic agent violapyrone C (**44**) consisted of a high yielding cyclization of the β-ketoester **43** (Scheme 7).[51] Likewise, a concise entry into the marine natural product wailupemycin G (**47**) features a gold-catalyzed ring closure after yet another gold-catalyzed furan-yne cyclization had set the naphthol unit in substrate **45**.[52]

The arguably most challenging applications are still the cyclizations leading to neurymenolide A (**1**)[1] and its 4-pyrone sibling **2**[2] already mentioned in the Introduction. They mandated selective transformation of one out of six or five π-systems in the cyclization precursors **48** and **50**, respectively, not counting the highly enolized β-ketoester units. As the skipped arrays render these substrates exceptionally labile, the successful and regioselective formations of **49** and **51** highlight the mildness of the new method. This aspect is further illustrated by the fact that the homoallylic bromide in **50** with latent "non-classical" carbocation reactivity as well as the fragile ketene-acetal substructure in **51** were not affected. In either total synthesis, a ring closing alkyne metathesis reaction served to forge the macrocyclic array.[53,54]

N-Heterocycles

In an attempt to extend this chemistry to the preparation of six-membered N-heterocycles, several readily available amide derivatives were screened to test how the N- rather than the O-atom of such substrates could be coaxed to serve as the internal nucleophile; a few selected examples are shown in Scheme 8.[55,56] For the sake of convenience, this screening was performed in the benzo-annulated series.

Although some literature reports suggest that N-tosylated amide derivatives can react as N-nucleophiles,[57] substrate **52** gave exclusively product **53** with the nitrogen substituent in



Scheme 8. Preliminary substrate screening: a) [(Johnphos)Au]SbF_6 (**61**) (5 mol%), HOAc, 66%; b) **61** (5 mol%), $MeNO_2/H_2O$ (4:1), 60 °C, 80%; c) Et_3OBF_4, CH_2Cl_2, Et_3N; d) **61** (5 mol%), CH_2Cl_2, 52% (**58**), 35% (**59**); e) AgOTs (5 mol%), DMEDA (5 mol%), $CHCl_3$, 0 °C→RT, 80% (**58**), <9% (**59**); f) BBr_3, CH_2Cl_2, 0 °C→RT, 96%; g) TMSI, MeCN, 80 °C, quant.

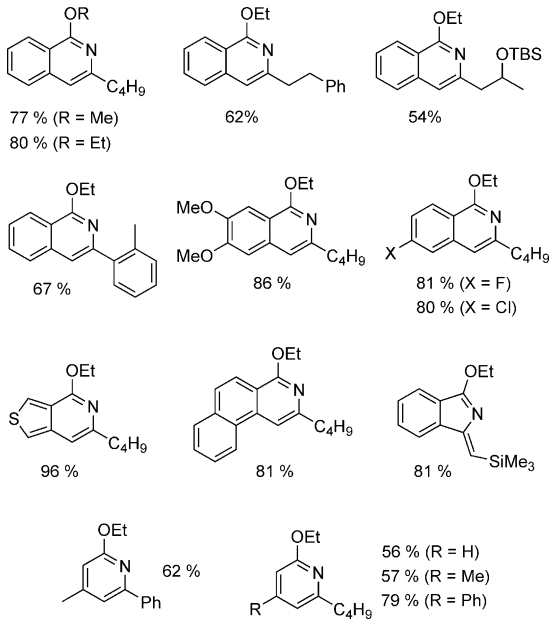


Figure 5. Selection of 2-alkoxypyridine and -isoquinoline derivatives formed by silver-catalyzed 6-*endo-dig* cyclization reactions (AgOTs, DMEDA, 5 mol% each, $CHCl_3$, 0 °C→RT); in all cases, small amounts of the isomeric 5-*exo-dig* products were formed which could be separated by flash chromatography; therefore, the reported yields refer to the pure samples of the depicted compounds.

an *exocyclic* position.[58] In contrast, oxazolines such as **54** furnished the corresponding isoquinolone derivatives on treatment with catalytic [(JohnPhos)Au]SbF_6 (**61**) in HOAc, but the N-substituent in **55** (or congeners) could not be cleaved under a variety of conditions. Gratifyingly though, the corresponding imidate **57**, which is readily formed from amide **56** on treatment with [$Et_3O{\cdot}BF_4$][59] followed by deprotonation of the resulting salt with Et_3N,[60] afforded the targeted isoquinoline derivative **58**;[61] however, a significant amount of the isomeric 5-*exo-dig* cyclization product **59** was also formed (**58**/**59** ≈1.5:1).[62] To avoid premature cleavage of the imidate group, the reaction was best carried out in neutral medium.

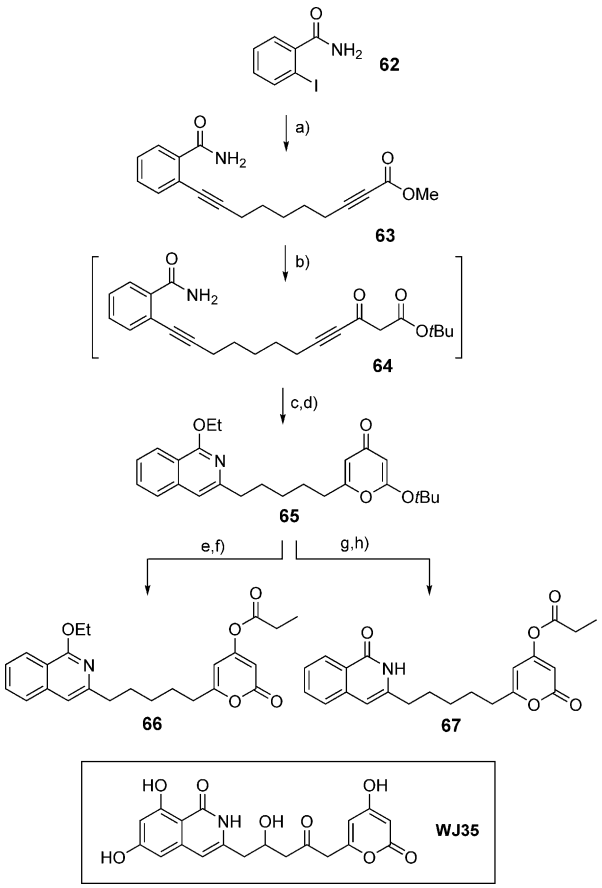
Although **58** and **59** are separable by flash chromatography, an optimization was deemed necessary. To this end, a large number of ligands, counterions and solvents were screened, but the product ratio did not vary by much. Therefore the screening was extended to other carbophilic catalysts, of which AgOTs in the presence of DMEDA furnished the best result.[63,64] In this case, less than 10% of **59** were formed, and analytically pure isoquinoline **58** could be isolated in 80% yield on a >1 gram scale. On treatment with either BBr_3 or TMSI, the corresponding 2-isoquinolone **60** was released in essentially quantitative yield.

Figure 5 shows an assortment of 2-alkoxypyridine derivatives which were obtained analogously. In all cases, small amounts of the regioisomers formed by 5-*exo-dig* ring closure were detected in the crude material, but could be readily removed on workup;[65] the indicated yields refer to pure samples of the depicted products. A notable exception, however, was observed in the cyclization of the silylated precursor, which furnished the 5-*exo*-product as the only detectable isomer in 81% yield.

Scheme 9 outlines a way to integrate the new pyrone and pyridine syntheses into a one-pot transformation. This model study was thought to probe whether aromatic polyketide derivatives such as the isoquinoline alkaloid WJ35[66] might be within reach of this methodology. To this end, a Sonogashira coupling between 2-iodobenzamide (**62**) and methyl deca-2,9-diynoate was used to form compound **63**, which was subjected to a Claisen condensation with excess *lithio* tert-butyl acetate. As the resulting product **64** turned out to be unstable, the crude material was treated with $Et_3O{\cdot}BF_4$ to form the corresponding imidate, which was activated with catalytic AgOTs/DMEDA to give the double-cyclization product **65** comprising a 4-pyrone and an isoquinoline nucleus; this sequence proceeded in 67% yield over three steps. Somewhat surprisingly, the use of BBr_3 allowed the pyrone ring to be selectively deprotected, whereas Me_3SiI cleaved both alkoxide substituents in **65**. For solubility reasons, either compound was isolated after O-acylation in the form of esters **66** and **67**.

Conclusion

Although carbophilic catalysts have fertilized many different areas of organic synthesis,[10,11] it is fair to say that they are particularly enriching for heterocyclic chemistry. Upon proper choice of the π-acid and the reaction conditions, it is possible to add a host of carbon-, oxygen, nitrogen or sulfur nucleo-



Scheme 9. a) Methyl deca-2,9-diynoate, $[(Ph_3P)_2PdCl_2]$ (3.5 mol%), CuI (8 mol%), Et_3N, DMF, 73%; b) *tert*-butyl acetate, LDA, THF, −78 °C, then **63**; c) Et_3OBF_4, CH_2Cl_2, Et_3N; d) AgOTs (10 mol%), DMEDA (10 mol%), $CHCl_3$, 0 °C, 68% (over three steps); e) BBr_3, CH_2Cl_2, 0 °C; f) propionic acid anhydride, Et_3N, CH_2Cl_2, 38% (over both steps); g) TMSI, MeCN, 60 °C; h) propionic acid anhydride, Et_3N, CH_2Cl_2, 77% (over both steps).

philes across the π-system of alkynes or allenes as particularly privileged substrates. The resulting adducts are usually identical or equivalent to the type of products traditionally prepared from carbonyl precursors by condensation reactions, which dominate classical heterocyclic chemistry.[67] Therefore, π-acid catalysis opens an orthogonal and, in many cases, complementary access route to a host of heterocyclic motifs of utmost importance.

This notion is corroborated by the results reported in this publication. Specifically, gold or silver-based catalysts are shown to provide 2-pyrones, 4-pyrones, 2-alkoxy-pyridines, 2-alkoxyisoquinolines and isoquinolones in good to excellent yields from readily available substrates, all of which were attained by well proven yet flexible methodologies. These transformations proceed under unprecedentedly mild conditions, which allow even exceptionally sensitive functionality to pass uncompromised. Moreover, they allow a single type of precursor to be converted into a 2-pyrone or a 4-pyrone, as one desires. Selected applications to the total synthesis of natural products of different degrees of complexity illustrate the broad scope and excellent application profile of the new methodology. Furthermore, the mechanistic understanding was enhanced by the isolation of relevant model complexes. In view of this sound basis, a number of extensions of the underlying concept can be envisaged, which we hope will materialize in the near future.

Experimental Section

All experimental details can be found in the Supporting Information. The material includes compound characterization, crystallographic abstracts and copies of spectra of new compounds. CCDC 1417652 (**12b**), 1417653 (**12c**), and 1417651 (**15**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Acknowledgements

Generous financial support by the MPG is gratefully acknowledged. We thank Dr. M. Corbet, Dr. W. Chaladaj, Dr. T. Fukuda, Dr. L. Hoffmeister and Dipl.-Chem. G. Pototschnig for exploratory studies or singular applications, as well as Mrs. Conny Wirtz, Julia Lingnau and Petra Phillipps for excellent NMR support. We are also grateful to Dr. Oliver Knopff, Firmenich SA, Geneva, for a sample of Romascone, and to Umicore AG & Co KG, Hanau, for a generous gift of various noble metal salts.

Keywords: diauration · gold · heterocycles · natural products · silver

[1] W. Chaładaj, M. Corbet, A. Fürstner, *Angew. Chem. Int. Ed.* **2012**, *51*, 6929 – 6933; *Angew. Chem.* **2012**, *124*, 7035 – 7039.
[2] L. Hoffmeister, T. Fukuda, G. Pototschnig, A. Fürstner, *Chem. Eur. J.* **2015**, *21*, 4529 – 4533.
[3] A. Fürstner, *Acc. Chem. Res.* **2014**, *47*, 925 – 938.
[4] E. P. Stout, A. P. Hasemeyer, A. L. Lane, T. M. Davenport, S. Engel, M. E. Hay, C. R. Fairchild, J. Prudhomme, K. Le Roch, W. Aalbersberg, J. Kubanek, *Org. Lett.* **2009**, *11*, 225 – 228.
[5] a) R. Kazlauskas, P. T. Murphy, R. J. Wells, A. J. Blackman, *Aust. J. Chem.* **1982**, *35*, 113 – 120; b) A. J. Blackman, J. B. Bremner, A. M. C. Paano, J. H. Skerratt, M. L. Swann, *Aust. J. Chem.* **1990**, *43*, 1133 – 1136; c) J. Shin, V. J. Paul, W. Fenical, *Tetrahedron Lett.* **1986**, *27*, 5189 – 5192; d) L. Murray, G. Currie, R. Capon, *Austr. J. Chem.* **1995**, *48*, 1485 – 1489.
[6] D. Song, G. Blond, A. Fürstner, *Tetrahedron* **2003**, *59*, 6899 – 6904.
[7] E. Suzuki, H. Sekizaki, S. Inoue, *J. Chem. Soc. Chem. Commun.* **1973**, 568.
[8] For reviews on 2-pyrones, see: a) J. S. Lee, *Mar. Drugs* **2015**, *13*, 1581 – 1620; b) A. Goel, V. J. Ram, *Tetrahedron* **2009**, *65*, 7865 – 7913; c) G. P. McGlacken, I. J. S. Fairlamb, *Nat. Prod. Rep.* **2005**, *22*, 369 – 385.
[9] For reviews on 4-pyrones, see: a) W. Wilk, H. Waldmann, M. Kaiser, *Bioorg. Med. Chem.* **2009**, *17*, 2304 – 2309; b) P. Sharma, K. J. Powell, J. Burnley, A. S. Awaad, J. E. Moses, *Synthesis* **2011**, 2865 – 2892; c) S. Yamamura, S. Nishiyama, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2025 – 2037.
[10] a) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410 – 3449; *Angew. Chem.* **2007**, *119*, 3478 – 3519; b) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208 – 3221.
[11] a) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395 – 403; b) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180 – 3211; c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326 – 3350.
[12] For different approaches to pyrones employing carbophilic catalysts, see: a) T. Luo, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2007**, *46*, 8250 – 8253; *Angew. Chem.* **2007**, *119*, 8398 – 8401; b) T. Luo, M. Dai, S.-L. Zheng, S. L. Schreiber, *Org. Lett.* **2011**, *13*, 2834 – 2836; c) T. Dombray, A. I. Blanc, J.-M. Weibel, P. Pale, *Org. Lett.* **2010**, *12*, 5362 – 5365; d) L. Anastasia, C. Xu, E.-I. Negishi, *Tetrahedron Lett.* **2002**, *43*, 5673 – 5676;

e) R. C. Larock, X. Han, M. J. Doty, *Tetrahedron Lett.* **1998**, *39*, 5713 – 5716; f) R. Manikandan, M. Jeganmohan, *Org. Lett.* **2014**, *16*, 652 – 655; g) see also: F. Bellina, M. Biagetti, A. Carpita, R. Rossi, *Tetrahedron Lett.* **2001**, *42*, 2859 – 2863.

[13] These substrates were readily prepared by Claisen condensation, cf. the Supporting Information.

[14] a) A. Leyva, A. Corma, *J. Org. Chem.* **2009**, *74*, 2067 – 2074; b) for triflimide as counterion in gold catalysis, see: N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133 – 4136.

[15] a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27 – 50; b) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461 – 1473.

[16] For a study suggesting that in some cases reactions claimed to be catalyzed by $(Ph_3P)AuOTf$ or related metal triflates might actually be catalyzed by HOTf generated in situ, see: a) D. C. Rosenfeld, S. Shekhar, A. Takemiya, M. Utsunomiya, J. F. Hartwig, *Org. Lett.* **2006**, *8*, 4179 – 4182; b) T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem.* **2011**, *76*, 9353 – 9361; c) N. Iqbal, G. Blakstad, A. Fiksdahl, *Tetrahedron* **2014**, *70*, 1317 – 1325.

[17] G. Seidel, C. W. Lehmann, A. Fürstner, *Angew. Chem. Int. Ed.* **2010**, *49*, 8466 – 8470; *Angew. Chem.* **2010**, *122*, 8644 – 8648.

[18] See also: a) M. Alcarazo, C. W. Lehmann, A. Anoop, W. Thiel, A. Fürstner, *Nat. Chem.* **2009**, *1*, 295 – 301; b) M. Alcarazo, K. Radkowski, G. Mehler, R. Goddard, A. Fürstner, *Chem. Commun.* **2013**, *49*, 3140 – 3142.

[19] For a stable platinated 4-hydroxy-2-pyrone derivative similar to **G**, see: L. Pandolfo, G. Paiaro, P. Ganis, G. Valle, P. Traldi, *Inorg. Chim. Acta* **1993**, *210*, 39 – 45.

[20] For in-depth studies on the mechanistic implications of diauration, see: a) A. Zhdanko, M. E. Maier, *Chem. Eur. J.* **2014**, *20*, 1918 – 1930; b) A. Zhdanko, M. E. Maier, *Organometallics* **2013**, *32*, 2000 – 2006; c) T. J. Brown, D. Weber, M. R. Gagné, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2012**, *134*, 9134 – 9137; d) D. Weber, T. D. Jones, L. L. Adduci, M. R. Gagné, *Angew. Chem. Int. Ed.* **2012**, *51*, 2452 – 2456; *Angew. Chem.* **2012**, *124*, 2502 – 2506.

[21] For related cases, in which addition of an acid led to substantial improvements, see the following and literature cited therein: a) W. Wang, G. B. Hammond, B. Xu, *J. Am. Chem. Soc.* **2012**, *134*, 5697 – 5705; b) W. T. Teo, W. Rao, C. J. H. Ng, S. W. Y. Koh, P. W. H. Chan, *Org. Lett.* **2014**, *16*, 1248 – 125; see also: c) R. E. M. Brooner, B. D. Robertson, R. A. Widenhoefer, *Organometallics* **2014**, *33*, 6466 – 6473.

[22] Au/H^+ co-catalysis has been used for enantioselective catalysis; for a recent review, see: S. M. Inamdar, A. Konala, N. T. Patil, *Chem. Commun.* **2014**, *50*, 15124 – 15135.

[23] Y. Zhu, B. Yu, *Angew. Chem. Int. Ed.* **2011**, *50*, 8329 – 8332; *Angew. Chem.* **2011**, *123*, 8479 – 8482.

[24] A. Zhdanko, M. E. Maier, *Chem. Eur. J.* **2013**, *19*, 3932 – 3942.

[25] For a discussion of how charge density is distributed over the ligand and the gold center, see: a) G. Seidel, A. Fürstner, *Angew. Chem. Int. Ed.* **2014**, *53*, 4807 – 4811; *Angew. Chem.* **2014**, *126*, 4907 – 4911; b) G. Seidel, B. Gabor, R. Goddard, B. Heggen, W. Thiel, A. Fürstner, *Angew. Chem. Int. Ed.* **2014**, *53*, 879 – 882; *Angew. Chem.* **2014**, *126*, 898 – 901; c) A. Fürstner, L. Morency, *Angew. Chem. Int. Ed.* **2008**, *47*, 5030 – 5033; *Angew. Chem.* **2008**, *120*, 5108 – 5111; d) G. Seidel, R. Mynott, A. Fürstner, *Angew. Chem. Int. Ed.* **2009**, *48*, 2510 – 2513; *Angew. Chem.* **2009**, *121*, 2548 – 2551.

[26] H. Schmidbaur, *Chem. Soc. Rev.* **1995**, *24*, 391 – 400.

[27] Y. Tang, J. Li, Y. Zhu, Y. Li, B. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 18396 – 18405.

[28] For a leading reference on the diauration of arenes, see the following an literature cited therein: J. E. Heckler, M. Zeller, A. D. Hunter, T. G. Gray, *Angew. Chem. Int. Ed.* **2012**, *51*, 5924 – 5928; *Angew. Chem.* **2012**, *124*, 6026 – 6030.

[29] A. Fürstner, C. Stimson, *Angew. Chem. Int. Ed.* **2007**, *46*, 8845 – 8849; *Angew. Chem.* **2007**, *119*, 9001 – 9005.

[30] For a previous synthesis, see: A. C. Giddens, L. Nielsen, H. I. Boshoff, D. Tasdemir, R. Perozzo, M. Kaiser, F. Wang, J. C. Sacchettini, B. R. Copp, *Tetrahedron* **2008**, *64*, 1242 – 1249.

[31] a) T. Hu, J. V. Schaus, K. Lam, M. G. Palfreyman, M. Wuonola, G. Gustafson, J. S. Panek, *J. Org. Chem.* **1998**, *63*, 2401 – 2406; b) A. Rentsch, M. Kalesse, *Angew. Chem. Int. Ed.* **2012**, *51*, 11381 – 11384; *Angew. Chem.* **2012**, *124*, 11543 – 11547.

[32] a) T. Doundoulakis, A. X. Xiang, R. Lira, K. A. Agrios, S. E. Webber, W. Sisson, R. M. Aust, A. M. Shah, R. E. Showalter, J. R. Appleman, K. B. Simonsen, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5667 – 5672; b) R. Lira, A. X. Xiang, T. Doundoulakis, W. T. Biller, K. A. Agrios, K. B. Simonsen, S. E. Webber, W. Sisson, R. M. Aust, A. M. Shah, R. E. Showalter, V. N. Banh, K. R. Steffy, J. R. Appleman, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6797 – 6800.

[33] M. A. Brook, Silicon in Organic, Organometallic, and Polymer Chemistry, Wiley, New York, **2000**.

[34] S. Flügge, A. Anoop, R. Goddard, W. Thiel, A. Fürstner, *Chem. Eur. J.* **2009**, *15*, 8558 – 8565.

[35] H. Schmidbaur, A. Schier, *Organometallics* **2010**, *29*, 2 – 23.

[36] a) I.-K. Lee, G.-S. Seo, N. B. Jeon, H.-W. Kang, B.-S. Yun, *J. Antibiot.* **2009**, *62*, 631 – 634; b) I.-K. Lee, J.-Y. Jung, Y.-H. Kim, B.-S. Yun, *J. Antibiot.* **2009**, *62*, 635 – 637; c) see also: I.-K. Lee, J.-Y. Jung, Y.-H. Kim, B.-S. Yun, *J. Antibiot.* **2010**, *63*, 263 – 266.

[37] For a review on styrylpyrones, see: I.-K. Lee, B.-S. Yun, *J. Antibiot.* **2011**, *64*, 349 – 359.

[38] J. P. Das, S. Roy, *J. Org. Chem.* **2002**, *67*, 7861 – 7864.

[39] L. Anastasia, E. Negishi, *Org. Lett.* **2001**, *3*, 3111 – 3113.

[40] W. Adam, C. R. Saha-Möller, M. Veit, B. Welke, *Synthesis* **1994**, 1133 – 1134.

[41] For an interesting recent study on the role of hispidine in fungal bioluminescence, see: K. V. Purtov, V. N. Petushkov, M. S. Baranov, K. S. Mineev, N. S. Rodionova, Z. M. Kaskova, A. S. Tsarkova, A. I. Petunin, V. S. Bondar, E. K. Rodicheva, S. E. Medvedeva, Y. Oba, Y. Oba, A. S. Arseniev, S. Lukyanov, J. I. Gitelson, I. V. Yampolsky, *Angew. Chem. Int. Ed.* **2015**, *54*, 8124 – 8128; *Angew. Chem.* **2015**, *127*, 8242 – 8246.

[42] H. C. Shen, J. Wang, K. P. Cole, M. J. McLaughlin, C. D. Morgan, C. J. Douglas, R. P. Hsung, H. A. Coverdale, A. I. Gerasyuto, J. M. Hahn, J. Liu, H. M. Sklenicka, L.-L. Wei, L. R. Zehnder, C. A. Zificsak, *J. Org. Chem.* **2003**, *68*, 1729 – 1735.

[43] H. Pauling, D. A. Andrews, N. C. Hindley, *Helv. Chim. Acta* **1976**, *59*, 1233 – 1243.

[44] a) D. A. Engel, G. B. Dudley, *Org. Biomol. Chem.* **2009**, *7*, 4149 – 4158; b) V. Cadierno, P. Crochet, S. E. García-Garrido, J. Gimeno, *Dalton Trans.* **2010**, *39*, 4015 – 4031.

[45] See the following for leading references and literature cited therein: a) M. Nukina, S. Marumo, *Tetrahedron Lett.* **1977**, *18*, 3271 – 3272; b) H. Nakajima, T. Ishida, Y. Otsuka, T. Hamasaki, M. Ichinoe, *Phytochemistry* **1997**, *45*, 41 – 45; c) H. Sheridan, A.-M. Canning, *J. Nat. Prod.* **1999**, *62*, 1568 – 1569; d) M. Solfrizzo, C. Vitti, A. De Girolamo, A. Visconti, A. Logrieco, F. P. Fanizzi, *J. Agric. Food Chem.* **2004**, *52*, 3655 – 3660.

[46] S. Koto, N. Morishima, Y. Mori, H. Tanaka, S. Hayashi, Y. Iwai, S. Zen, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2301 – 2303.

[47] a) R. R. Schmidt, J. Kast, *Tetrahedron Lett.* **1986**, *27*, 4007 – 4010; b) J. Kast, M. Hoch, R. R. Schmidt, *Liebigs Ann. Chem.* **1991**, 481 – 485.

[48] C. Nájera, M. Yus, *Tetrahedron Lett.* **1989**, *30*, 173 – 176.

[49] H. J. Bestmann, H. Frey, *Liebigs Ann. Chem.* **1980**, 2061 – 2071.

[50] This transformation resembles a substitution previously observed with 2-formylglycal derivatives, cf. G. K. Rawal. S. Rani, N. Kumari, Y. D. Vankar, *J. Org. Chem.* **2009**, *74*, 5349 – 5355.

[51] J. S. Lee, J. Shin, H. J. Shin, H.-S. Lee, Y.-J. Lee, H.-S. Lee, H. Won, *Eur. J. Org. Chem.* **2014**, 4472 – 4476.

[52] Y. Chen, L. Wang, N. Sun, X. Xie, X. Zhou, H. Chen, Y. Li, Y. Liu, *Chem. Eur. J.* **2014**, *20*, 12015 – 12019.

[53] a) A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 2794 – 2819; *Angew. Chem.* **2013**, *125*, 2860 – 2887; b) A. Fürstner, P. W. Davies, *Chem. Commun.* **2005**, 2307 – 2320.

[54] a) J. Heppekausen, R. Stade, A. Kondoh, G. Seidel, R. Goddard, A. Fürstner, *Chem. Eur. J.* **2012**, *18*, 10281 – 10299; b) J. Heppekausen, R. Stade, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 11045 – 11057; c) P. Persich, J. Llaveria, R. Lhermet, T. de Haro, R. Stade, A. Kondoh, A. Fürstner, *Chem. Eur. J.* **2013**, *19*, 13047 – 13058.

[55] For π-acid catalyzed approaches to isoquinolines starting from azide derivatives, see: a) Z. Huo, Y. Yamamoto, *Tetrahedron Lett.* **2009**, *50*, 3651 – 3653; b) Y.-N. Niu, Z.-Y. Yan, G.-L. Gao, H.-L. Wang, X.-Z. Shu, K.-G. Ji, Y.-M. Liang, *J. Org. Chem.* **2009**, *74*, 2893 – 2896; c) V. R. Batchu, D. K. Barange, D. Kumar, B. R. Sreekanth, K. Vyas, E. A. Reddy, M. Pal, *Chem. Commun.* **2007**, 1966 – 1968.

[56] For approaches using aldoximes as the internal nucleophiles, see: a) Q. Xiao, D. Zheng, Q. Ding, J. Wu, *Tetrahedron* **2013**, *69*, 5119 – 5122; b) H. Gao, J. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 85 – 88; c) T. Wang, R. Li, D. Yu, C. Gu, F. Xiong, Z. Chen, *Synthesis* **2014**, *46*, 3213 – 3220.

[57] a) S. Nicolai, C. Piemontesi, J. Waser, *Angew. Chem. Int. Ed.* **2011**, *50*, 4680 – 4683; *Angew. Chem.* **2011**, *123*, 4776 – 4779; b) see also: A. Gimeno, A. B. Cuenca, M. Medio-Simón, G. Asensio, *Adv. Synth. Catal.* **2014**, *356*, 229 – 236; c) even regular amides were suggested to act as N-nucleophiles in gold catalyzed reactions, see: S. Obika, Y. Yasui, R. Yanada, Y. Takemoto, *J. Org. Chem.* **2008**, *73*, 5206 – 5209.

[58] Compare: a) G. Liu, Y. Zhou, D. Ye, D. Zhang, X. Ding, H. Jiang, H. Liu, *Adv. Synth. Catal.* **2009**, *351*, 2605 – 2610; b) Y. Long, Z. She, X. Liu, Y. Chen, *J. Org. Chem.* **2013**, *78*, 2579 – 2588.

[59] H. Meerwein, *Org. Synth.* **1966**, *46*, 113 – 115.

[60] L. Weintraub, S. R. Oles, N. Kalish, *J. Org. Chem.* **1968**, *33*, 1679 – 1681.

[61] For related cyclizations of imidates generated in situ from nitrile precursors, see: a) J. Li, L. Chen, E. Chin, A. S. Lui, H. Zecic, *Tetrahedron Lett.* **2010**, *51*, 6422 – 6425; b) R. M. Singh, R. Kumar, N. Sharma, M. Asthana, *Tetrahedron* **2013**, *69*, 9443 – 9450.

[62] For similar issues, see: a) F. M. Irudayanathan, J. Noh, J. Choi, S. Lee, *Adv. Synth. Catal.* **2014**, *356*, 3433 – 3442; b) L.-M. Wei, C.-F. Lin, M.-J. Wu, *Tetrahedron Lett.* **2000**, *41*, 1215 – 1218.

[63] Reviews: a) *Silver in Organic Chemistry* (Ed.: M. Harmata), John Wiley & Sons, Hoboken, N. J., **2010**; b) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* **2008**, *108*, 3174 – 3198; c) J.-M. Weibel, A. Blanc, P. Pale, *Chem. Rev.* **2008**, *108*, 3149 – 3173.

[64] $PtCl_2$ in CH_2Cl_2 gave similarly favorable results; in view of the much higher price, this hit was not optimized any further. For previous use of Pt(+2) catalysis in heterocycle synthesis from this laboratory, see: a) A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120*, 8305 – 8314; b) A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863 – 11869; c) V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556 – 4575; d) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024 – 15025; e) A. Fürstner, E. K. Heilmann, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 4760 – 4763; *Angew. Chem.* **2007**, *119*, 4844 – 4847.

[65] A sterically bulky or aromatic substituent at the triple bond seems to favor the 5-*exo-dig* pathway.

[66] a) W. Zhang, B. I. Wilke, J. Zhan, K. Watanabe, C. N. Bobby, Y. Tang, *J. Am. Chem. Soc.* **2007**, *129*, 9304 – 9305; b) W. Zhang, B. D. Ames, S.-C. Tsai, Y. Tang, *Appl. Environ. Microbiol.* **2006**, *72*, 2573 – 2580.

[67] J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 4th ed., Blackwell Publishing, Oxford, **2002**.

Received: August 27, 2015
Published online on November 23, 2015