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ARTICLE *in* CHEMISTRY - A EUROPEAN JOURNAL · MARCH 2013

Impact Factor: 5.73 · DOI: 10.1002/chem.201202225 · Source: PubMed

CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201202225

Dual Hard/Soft Gold Catalysis: Intermolecular Friedel–Crafts-Type α-Amidoalkylation/Alkyne Hydroarylation Sequences by *N*-Acyliminium Ion Chemistry

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Abstract: Gold catalysts have been applied in cascade-type reactions for the synthesis of different nitrogen-based compounds. The reactions likely proceed by a new gold-catalyzed cascade intermolecular α-amidoalkylation/intramolecular carbocyclization cascade process by unifying both the σ- and π-Lewis acid properties of the gold salts. In the first part of this report we show that the σ-Lewis acidity of gold(I) and gold(III) could be exploited to efficiently catalyze the nucleophilic substitution of various alkoxy- and acetoxylactams. The reaction was found to be applicable to a wide range of cyclic *N*-acyliminium ion precursors and various nucleophiles, including allyltrimethylsilane, silyl enol ethers, arenes, and active methylene derivatives. As a logical progression of this study, a combined hard/soft binary catalytic gold system was then used to implement an unprecedented tandem intermolecular Friedel–Crafts amidoalkylation/intramolecular hydroarylation sequence allowing an expedient access to new, complex, fused polyheterocyclic structures from trivial materials.

Keywords: gold · homogeneous catalysis · hydroarylation · nitrogen heterocycles · reaction mechanisms

Introduction

In recent years, gold(III) and gold(I) cationic complexes have been shown to display eminent catalytic activity under mild conditions, rendering them attractive reagents in organic synthesis.[1] In particular, gold catalysts have proven to be powerful alkynophilic Lewis acids by activating π systems towards nucleophilic attack, allowing the formation of new C–C, C–O, C–N, and C–S bonds. Recent calculations have revealed that gold ions are also σ-Lewis acids.[2] However, even if their peculiar aptitude for interaction with oxygen-based electrophiles has long been known,[3] gold salts/complexes have been mainly used as catalytic carbophilic activators. Reactions triggered by σ-Lewis acid activation modes have been relatively ignored and the synthetic potential of this complementary approach has risen to prominence only quite recently. Early literature reports in this area were mainly devoted to Lewis acid activation of carbonyl compounds,[3,4] but recent reports have shown that Au^{I} and Au^{III} salts are also competent catalysts in the mediation of dehydrative couplings of activated π alcohols (and their ether or ester derivatives) with many types of carbo- and heteronucleophiles.[5] Highly reactive substrates such as doubly π-activated alcohols, that is, precursors of well-stabilized cations, have generally been used in intermolecular reactions[6a–n] whereas gold-catalyzed intramolecular dehydrative couplings with good neutral nucleophiles (indoles, heteronucleophiles) tolerated less reactive substrates such as simple primary allylic alcohols.[6o,p] To broaden the general scope of gold catalysis, it is important to expand the range of substrates and functional groups that can be activated by gold complexes.[7] *N,O*-Acetals are weak yet useful electrophiles that give a myriad of interesting compounds upon acidic activation and subsequent interception of the highly reactive *N*-acyliminium ion intermediates by an internal or external nucleophile.[8] Our continuing interest in developing safer C–C bond-forming reactions based on *N*-acyliminium ion chemistry[9] has led us to postulate that the oxophilicity of gold catalysts might be applicable to the α-amidoalkylation of *N,O*-acetals.[10] More importantly, the high construction flexibility of *N,O*-acetal frameworks and the particular ease of access of *N*-propargyl and homopropargyl counterparts[11] raises the prospect that engineering an unprecedented gold-catalyzed intermolecular α-amidoalkylation/intramolecular carbocyclization cascade process by unifying both the σ- and π-Lewis acid properties of gold salts might be feasible (Scheme 1).[12,13] Such types of cascade transformations would offer a straightforward access to complex, fused polyheterocyclic structures from trivial materials and also con-

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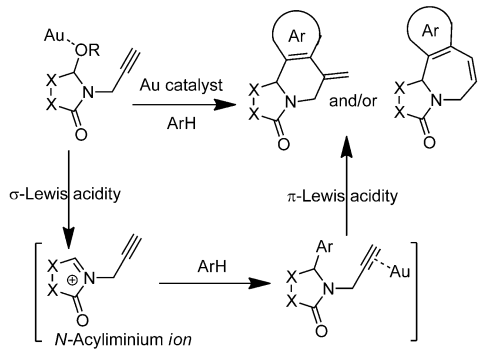
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201202225. Further experimental details are provided.



Scheme 1. Proposed one-pot gold-catalyzed Friedel–Crafts/hydroarylation reaction of alkoxylactams.

tribute to the rapid emergence of multicatalytic cascade and tandem transformations.[14]

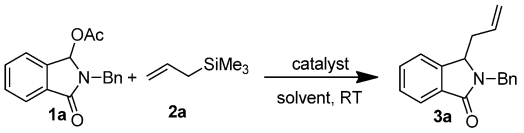
We report herein that hard (ligand-free) gold(I) and gold(III) salts are efficient catalysts for *N*-acyliminium ion chemistry by demonstrating their ability to accommodate a large spectrum of *N,O*-acetal/neutral carbon nucleophile combinations. In this paper we also report the first examples of a one-pot gold-catalyzed α-amidoalkylation/intramolecular hydroarylation sequence, showcasing that the marriage of σ- and π-Lewis acidity within gold catalysis can be useful in the context of *N*-acyliminium ion chemistry.[15]

Results and Discussion

We have previously shown that triflate- and triflimidate-based superacid catalysts are highly efficient for the α-amidoalkylation of various silicon-based and neutral (C–H) nucleophiles.[9] To assess the capacity of gold catalysts to rival these methods, various Au^{III}, Au^{I}, and Ag^{I} catalysts were initially screened for the intermolecular nucleophilic substitution of acetoxylactam **1a** by using allyl trimethylsilane **2a** as a nucleophile (Table 1). For comparison purposes, some of our results obtained by using other Lewis or Brønsted acids are presented in entries 1–3.[9a]

Neutral gold chloride (AuCl) did not promote any transformation, irrespective of the solvent and the amount of catalyst, and the starting material **1a** was fully recovered even after a prolonged reaction time (entry 4). An interesting solvent effect was observed with $AuCl_3$ in acetonitrile but this still requires further investigation (entries 5 versus 6).[16] Remarkably, switching to the hard, cationic Au^{I} and Au^{III} triflate salts, produced in situ by premixing gold(I) and (III) chlorides and silver triflate,[17] led to the rapid formation of **3a** in excellent yields, irrespective of the solvent used (entries 7–9). In particular, the reactions with 1 mol% of AuOTf (entry 8) demonstrated that suitable gold catalysts can display similar performances to super Brønsted and Lewis acids (cf. entry 8 with entries 2 and 3). Shorter reaction times were logically required in the reactions catalyzed by $Au(OTf)_3$, which reflects the higher Lewis acidity of gold-

Table 1. Optimization of the gold-catalyzed α-amidoalkylation of acetoxylactam **1a**.



Entry	Catalyst (Amount [mol%])	Solvent	Time	Yield [%]
1	TIPSOTf (5)	CH_2Cl_2	30 min	88
2	Tf_2NH (1)	CH_3CN	1 h	97[b]
3	$Sn(NTf_2)_4$ (1)	CH_3CN	1 h	98[b]
4	AuCl (10)	CH_2Cl_2/CH_3CN	24 h	NR
5	$AuCl_3$ (2)	CH_2Cl_2	8 h	traces
6	$AuCl_3$ (2)	CH_3CN	45 min	57
7	AuOTf (2)[a]	CH_2Cl_2/CH_3CN	20 min	93[c]/95[d]
8	AuOTf (1)[a]	CH_2Cl_2/CH_3CN	30 min	93[c]/95[d]
9	$Au(OTf)_3$ (2)[a]	CH_2Cl_2/CH_3CN	15 min	94[c]/98[d]
10	AgOTf (10)	CH_2Cl_2/CH_3CN	24 h	NR
11	TfOH (2)	CH_2Cl_2	45 min	92
12	$[(Ph_3P)AuOTf]$ (2)[a]	CH_2Cl_2	1 h	90
13	$[(Ph_3P)AuOTf]$ (2)[a]	CH_3CN	1 h	NR
14	$[\{(PhO)_3P\}AuOTf]$ (2)[a]	CH_2Cl_2	1 h	95
15	$[\{(PhO)_3P\}AuOTf]$ (2)[a]	CH_3CN	1 h	NR
16	$[(Ph_3P)AuNTf_2]$ (2)	CH_2Cl_2	2 h	84

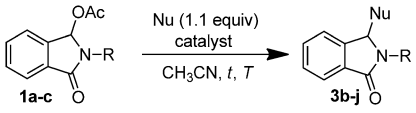
[a] $AuOTf = AuCl + AgOTf$, $Au(OTf)_3 = AuCl_3 + 3AgOTf$, $[(Ph_3P)AuOTf] = (Ph_3P)AuCl + AgOTf$, and $[\{(PhO)_3P\}AuOTf] = [\{(PhO)_3P\}AuCl] + AgOTf$. [b] Unpublished results, reaction time unoptimized. [c] Isolated yield in CH_2Cl_2. [d] Isolated yield in CH_3CN.

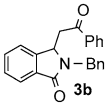
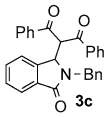
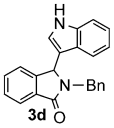
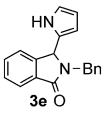
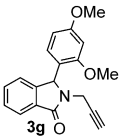
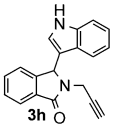
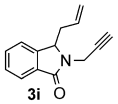
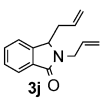
(III) salts. The reaction in the presence of AgOTf left the substrate untouched, which confirms that these alkylations are not promoted by silver catalysts (entry 10). Recognizing that a combination of AuCl and AgOTf might incidentally provide TfOH, which could act as a precatalyst by quickly generating TMSOTf as the true catalyst,[9a,c] a control experiment was performed by using 2 mol% of TfOH. The allylated adduct **3a** was produced in high yield, although a longer time was required than for the gold-catalyzed reaction (45 min in entry 11 versus 20 min in entry 7). These results show that the contribution of a silyl Lewis acid mechanism may compete to some extent with the gold catalysis pathway in the reactions presented in entries 7–9. The softer reagents $[(Ph_3P)AuOTf]$ and $[\{(PhO)_3P\}AuOTf]$ in CH_2Cl_2 also gave high yields of **3a**, but longer reaction times were logically required (entries 12 and 14). As expected, a more coordinating solvent such as acetonitrile totally inhibited the reaction with these two weakly electrophilic catalysts (Table 1, entries 13 and 15). Changing the nature of the weakly coordinating counterion from OTf^- to NTf_2^-[18] had a negative effect on the conversion rate of substrate **1a** because the yields of **3a** diminished and the reaction times increased (Table 1, entry 16 versus 12). This counterion effect is in stark contrast to our previous studies[9b] and cannot be accounted for at this stage. However, it does support the idea that this reaction would be mainly governed by gold catalysis rather than silyl Lewis acid catalysis. The use of allylpinacolborane instead of allyltrimethylsilane under the optimized conditions (2 mol% of AuOTf in acetonitrile) did not furnish **3a**, even after a prolonged reaction time (5 h), and the parent hydroxylactam was recovered quantitatively

(results not shown), which demonstrates the distinct advantage of allylsilanes in catalytic *N*-acyliminium ion chemistry.[9]

With two optimal catalysts and reaction conditions in hand, we next examined the α-amidoalkylation reaction with substrates **1a–c** in the presence of various nucleophiles; the most representative results are illustrated in Table 2. The reaction tolerates a range of aromatic and nonaromatic

Table 2. Scope of the gold-catalyzed α-amidoalkylation of acetoxylactams **1a–c**.



Entry	Catalyst[a]	Nu	*t*, *T*	Product	Yield [%]
1	AuOTf	 **2b**	45 min, 50 °C	 **3b**	82
2	AuOTf	 **2c**	1 h, RT	 **3c**	85/84[b]
3	AuOTf	 **2d**	5 min, RT	 **3d**	83[c]
4	$Au(OTf)_3$	 **2e**	5 min, RT	 **3e**	73
5	$Au(OTf)_3$	 **2f**	2.5 h, 50 °C	 **3f**	85
6	AuOTf	 **2g**	18 h, RT	 **3g**	89
7	AuOTf	**2d**	5 min, RT	 **3h**	96
8	$AuNTf_2$	**2d**	30 min, RT	**3h**	92[c]
9	$AuSbF_6$	**2d**	30 min, RT	**3h**	82[c,d]
10	AuOTf	**2a**	15 min, RT	 **3i**	98
11	AuOTf	**2a**	30 min, RT	 **3j**	96

[a] 2 mol% catalyst was used. AuOTf = AuCl + AgOTf, $Au(OTf)_3$ = AuCl + 3AgOTf, $AuNTf_2$ = AuCl + $AgNTf_2$, and $AuSbF_6$ = AuCl + $AgSbF_6$. [b] Reaction conditions: **1a** (10 mmol), **2c** (11 mmol), and AuOTf (2 mol%) over 1.25 h; 1 h is for the small-scale experiment; the larger scale experiment was completed with 1.25 h. [c] Reaction carried out in CH_2Cl_2. [d] 7% of the acetoxylactam **1c** was recovered after flash column chromatography.

carbon nucleophiles and is not altered by the nature of the N-protecting group, affording the expected adducts **3b–j** in good-to-excellent yields (73–98%). For some unknown reason, trimethylsilyl enol ether **2b** derived from acetophenone required harsher reaction conditions to undergo smooth conversion than the Tf_2NH- and R_3SiOTf-catalyzed variants.[9b,c] Although no reaction occurred at room temperature in CH_3CN, the expected product **3b** was isolated in 82% yield at a higher temperature (entry 1). This result again seems to exclude a significant contribution of a silyl Lewis acid pathway in these gold-catalyzed amidoalkylation reactions.

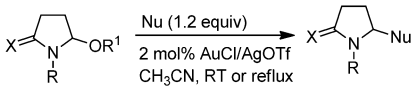
Importantly, the AuOTf protocol can be applied to the gram-scale synthesis of derivatives **3** with comparative efficiency. This is exemplified by the successful coupling reaction of **1a** (10 mmol) with the weakly nucleophilic dibenzoylmethane (**2c**; 11 mmol), which, in the presence of 2 mol% of AuOTf, afforded **3c** in 84% yield after 1.25 h (entry 2). With C–H aromatic nucleophiles **2d–g**, Friedel–Crafts arylation occurred to afford compounds **3d–h** in good yields (Table 2, entries 3–9). With the highly nucleophilic indole (**2d**) and pyrrole (**2e**),[19] the reactions proceeded remarkably smoothly and were completed in less than 5 min at room temperature (Table 2, entries 3, 4, and 7). As expected, 2-bromothiophene (**2f**) and 1,3-dimethoxybenzene (**2g**) were found to be less reactive in the amidoalkylation process and thus required longer reaction times and a higher temperature (50 °C for **2f**; Table 2, entries 5 and 6). Substrate **1c**, which incorporates a propargylamino motif, was alkylated with high chemoselectivity (entries 6–10), and the reactions with the best π nucleophiles[19a] proceeded very quickly (entries 7–10). This is remarkable given the multiple reaction possibilities of **1c** and its alkylated adducts **3g–i**, including intermolecular hydroarylation,[20] intramolecular oxacyclization of amide alkynes,[21] cyclization/fragmentation/recyclization,[22,23] as well as intramolecular hydroarylation (in the cases of **3g**,**h**, Scheme 1)[24] or enyne cycloisomerization (in the case of **3i**).[25,26]

Moreover, the results in entries 7–9 highlight the distinct advantage of AuX (X = OTf, NTf_2, and SbF_6) over Brønsted superacids as catalysts in these alkylative transformations. Indeed, poor conversion (ca. 20% conv.) was observed only in the presence of 2 mol% of Tf_2NH under similar conditions for the indoylation of **1c**. This may be a result of the distinct ability of gold to engage in coordination with both the alkyne and one oxygen atom of the acetate leaving group,[27] thus enabling facile generation of the transient *N*-acyliminium. Conversely, competitive protonation of the triple bond and/or the indolic nitrogen by Tf_2NH may be unproductive in generating the cation. In addition, the counterion effect seen in this AuX-catalyzed Friedel–Crafts reaction ($OTf > NTf_2 > SbF_6$, entries 7–9) seemingly suggests the dominance of a Lewis acid type mechanism because an inverse trend would be expected if the catalysis was governed by a Brønsted acid.

To further demonstrate the general applicability of this methodology, we next investigated the alkylation of less

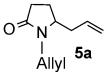
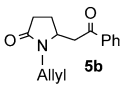
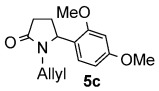
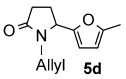
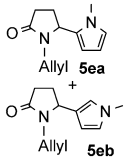
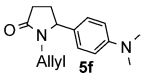
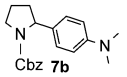
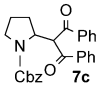
robust alkoxylactams such as **4** and **6** with a series of nucleophiles by using the Au^I optimal conditions described above (Table 3). Typical carbon-centered nucleophiles, exemplified by **2a**—**c**, reacted satisfactorily with both *N*,*O*-acetals (entries 1, 2, 7, and 9).

Table 3. Scope of the gold-catalyzed α-amidoalkylation of alkoxylactams **4** and **6** with various nucleophiles.



4 R = Allyl, R^1 = Et, X = O **5a-f**

6 R = Cbz, R^1 = Me, X = H,H **7a-c**

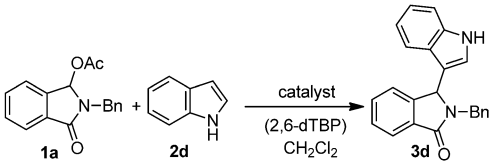
Entry	Nu	*t*, *T*	Product	Yield [%]
1[a,b]	**2a**	18 h, 40 °C	 **5a**	>99
2	**2b**	45 min, RT	 **5b**	64
3	**2g**	3 h, RT	 **5c**	81
4	 **2h**	1.5 h, RT	 **5d**	57
5[b]	 **2i**	5 min, RT	 **5ea** + **5eb**	61[c]
6	 **2j**	18 h, RT	 **5f**	60
7[a,b]	**2a**	5 min, RT	 **7a**	89
8	**2j**	1.5 h, reflux	 **7b**	69
9	**2c**	30 min, RT	 **7c**	66

[a] Conducted with 2 equiv of the nucleophile. [b] Reaction carried out in CH_2Cl_2. [c] Isolated as a mixture of regioisomers in a 1:1.5 ratio.

Heteroaromatic rings were again suitable nucleophiles for this reaction: 2-Methylfuran (**2h**) afforded **5d** in 57% yield and *N*-methylpyrrole (**2i**) delivered regioisomers **5ea** and **5eb** in 61% combined yield (ratio 1:1.5; entries 4 and 5). Finally, the reaction of *N*,*N*-dimethylaniline (**2j**) with both pyrrolidone **4** and pyrrolidine **6** aminals produced the cross-coupling products with *para* selectivity in 60 and 69% yields, respectively (entries 6 and 8). Note that most of these reactions were carried out in CH_3CN, but some were performed in CH_2Cl_2 (entries 1, 5, and 7) simply to demonstrate that the process could tolerate either solvent. Note also that although Au^I and Au^{III} are equally efficient in catalyzing the α-amidoalkylation reaction, the AuCl precatalyst is preferred as it is less hygroscopic than $AuCl_3$ and is thus easier to weigh and handle in small-scale experiments.

As previously discussed, it is reasonable to think that gold catalysis dominates over silyl catalysis in the amidoalkylation of the silicon-based nucleophiles described herein. In line with this, we next embarked on a mechanistic study aimed at probing the identity of the catalytic species, Lewis or Brønsted acid, involved in the reactions with C–H nucleophiles.[28] Indole (**2d**) was chosen as a representative model and its reaction with **1a** was studied under a variety of reaction conditions, notably including the use of 2,6-di-*tert*-butylpyridine (2,6-DTBP) as a proton scavenger (Table 4).

Table 4. Comparison of Lewis and Brønsted acid catalysts in the α-amidoalkylation of acetoxylactam **1a**.



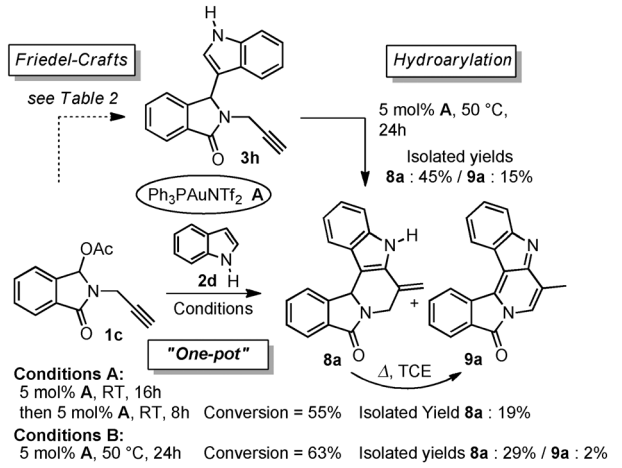
Entry	Catalyst (Amount [mol%])	Additive (Amount [mol%])	Time	Yield [%][a]
1	–	–	24 h	0
2	HOTf (2)	–	30 min	100
3	HOTf (2)	2.6-DTBP[b] (2)	72 h	0
4	AuOTf (2)[c]	–	5 min	100
5	AuOTf (2)[c]	2.6-DTBP (2)	5 min	14
6	AuOTf (2)[c]	2.6-DTBP (2)	2 h	100

[a] NMR conversion yields are given. [b] 2,6-DTBP = 2,6-di-*tert*-butylpyridine. [c] AuOTf = AuCl + AgOTf

It was found that the intermolecular nucleophilic substitution reaction of **2d** in CH_2Cl_2 in the presence of 2 mol% of HOTf at room temperature provided adduct **3d** in almost quantitative NMR yield within 30 min (Table 4, entry 2). The same reaction catalyzed by 2 mol% of AuOTf occurred six-fold faster with comparative efficiency (entry 4 versus 2). As expected, the addition of 2 mol% of 2,6-DTBP completely inhibited the Brønsted acid catalyzed amidoalkylation reaction (Table 4, entry 3), whereas the addition of 2 mol% of 2,6-DTBP to 2 mol% of AuOTf still resulted in the formation of the product **3d**, albeit at a lower rate (2 h versus 5 min for full conversion, entries 4–6). Considering that the activity of the gold catalyst in the nucleophilic substitution step is diminished but not inhibited by the presence of 2,6-DTBP, combined with the fact that a higher rate was observed for the AuOTf-catalyzed α-amidoalkylation of indole (30 versus 5 min, entry 2 versus 4), we believe that the reactions developed herein are mainly gold-catalyzed, but that a Lewis acid (Au) assisted (LBA) Brønsted acid (HOTf) catalysis[29] may operate[30] to some extent.

Finally, we started to evaluate the one-pot α-amidoalkylation/hydroarylation sequence and our preliminary results are described herein. As indole (**2d**) gave excellent results

for the α-amidoalkylation step, it was chosen as a representative nucleophile for this transformation (Scheme 2).[31] In addition to demonstrating a novel type of cascade catalytic

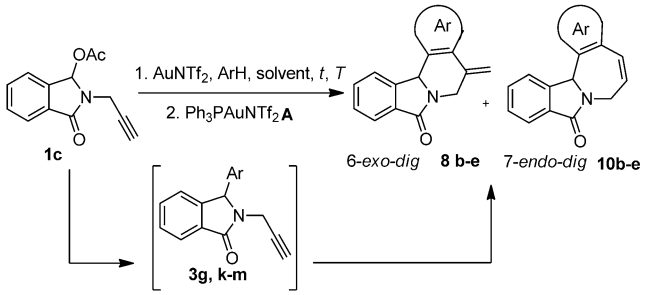


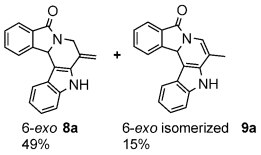
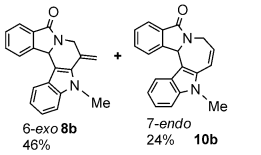
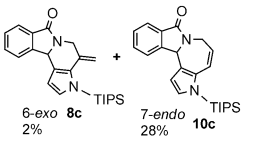
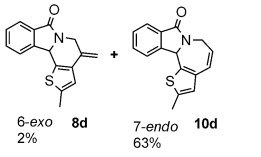
Scheme 2. One-pot gold-catalyzed Friedel–Crafts/hydroarylation reaction of **1c**.

transformation, this effort would produce novel polyheterocyclic structures containing both an isoindolone and an indole, two important motifs in medicinal chemistry.[32,33] Before exploring the one-pot procedure, we decided to test the feasibility of the hydroarylation reaction on adduct **3h** incorporating the appropriate *N*-propargyl moiety. An array of simple gold salts, including those that were effective in the alkylation step, were initially surveyed; $AuCl_3$, AuCl, AuOTf, $Au(OTf)_3$, $[(Ph_3P)AuOTf]$, and $[\{(PhO)_3P\}AuOTf]$ all showed no or low activity in the cyclization process. In most cases only small amounts (<10%) of cyclic products, namely *exo*-methylenebenzoindolizinone **8a** and isomerized benzoindolizinone **9a**, were indeed observed irrespective of the solvent or the temperature. We found that treatment of **3h** with 5 mol% of $[(PPh_3)AuNTf_2]$[18a,34] in 1,2-dichloroethane (DCE) at 50°C led to the formation of a 3:1 ratio of the two expected benzoindolizines **8a** and **9a** in 45 and 15% isolated yields, respectively.

Encouraged by the formation of these polycyclic compounds, we attempted the one-pot preparation of these indolizinones directly from acetoxylactam **1c** (Table 5). Initially, **1c** and 1.1 equiv of indole (**2d**) in DCE at room temperature were subjected to the portionwise addition of $[(Ph_3P)AuNTf_2]$ over 24 h (5 mol%, 16 h at RT, then again 5 mol%, 8 h at RT). Compound **8a** was obtained in 19% isolated yield along with 45% of the recovered acetoxylactam **1c**, which emphasizes the fact that hydroarylation may interfere with Friedel–Crafts alkylation. This preliminary attempt highlights the great challenge associated with our desired sequence in comparison with the high-yielding sequence previously developed by Liu and co-workers starting from enynol substrates.[13a] An encouraging 31% combined yield of **8a** (29%) and **9a** (2%) was obtained when the reaction was conducted in DCE at 50°C for 24 h with 5 mol% $[(Ph_3P)AuNTf_2]$, although a significant amount of **1c** was again recovered (37%).

Table 5. Scope of the one-pot gold-catalyzed α-amidoalkylation/hydroarylation of acetoxylactam **1c** with various nucleophiles.



Entry	ArH	Reaction conditions	Products[a]
1		2 mol% AuOTf,[b] 5 min, RT, then (5+5) mol% cat. **A**, 3 h+3 h, DCE, 50°C	 6-*exo* **8a** 49% 6-*exo* isomerized **9a** 15%
2		2 mol% $AuNTf_2$,[b] 1 h, RT, then (5+5) mol% cat. **A**, 2 h+1 h, DCM, reflux	 6-*exo* **8b** 46% 7-*endo* **10b** 24%
3		2 mol% $AuNTf_2$,[b] 1 h, RT, then (5+5) mol% cat. **A**, 1.5 h+1 h, DCM, RT	 6-*exo* **8c** 2% 7-*endo* **10c** 28%
4		2 mol% $AuNTf_2$,[b] 1 h, RT, then (5+5) mol% cat. **A**, 2 h+1 h, DCE, 50°C	 6-*exo* **8d** 2% 7-*endo* **10d** 63%

[a] Isolated yields. [b] AuOTf = AuCl + AgOTf and $AuNTf_2$ = AuCl + $AgNTf_2$.

Recognizing the limitations displayed by a single gold catalyst approach, we sought to implement a more efficient procedure for this tandem amidoalkylation/hydroarylation sequence by combining the use of a hard/soft binary catalytic gold system. Having previously identified AuOTf as an excellent catalyst for the amidoalkylation reaction, it was then combined with $[(PPh_3)AuNTf_2]$ in a one-pot manner. After further optimization, this procedure led to an acceptable compromise between hydroarylation and α-amidoalkylation efficiency. When carrying out the sequence in DCE, first in the presence of AuOTf (2 mol%, 5 min at RT) followed by the portionwise addition of $[(Ph_3P)AuNTf_2]$ (2 mol% AuOTf, 5 min at RT followed by 5 mol% $[(Ph_3P)AuNTf_2]$, 3 h at 50°C, then 5 mol%, 3 h at 50°C), compounds **8a** and **9a** were isolated in a synthetically useful

combined yield of 64% (Table 5, entry 1). This set of results indicates that to achieve good reaction yields it is crucial to first complete the Friedel–Crafts alkylation before the hydroarylation reaction begins. Also note that subsequent heating in DCE alone led to the rapid isomerization of **8a** into **9a**.[35] A detailed analysis of all the results thus demonstrates that appropriate selection of the gold catalyst system could selectively stop the reaction at the alkylation stage (see Table 2, entries 7–9) or allow continuation to the alkylation/hydroarylation sequence.

Having established the effectiveness of this binary catalytic system for the cascade reaction with indole as a model binucleophile (Scheme 2 and Table 5, entry 1), we next started to explore its scope by varying the nature of the aromatic donor. Our preliminary results are reported in Table 5, entries 2–4. They show that the *exo*/*endo* selectivity of the reaction is highly dependent upon the nature of the aromatic element, thereby underlying exciting future discoveries in these kinds of reactions. Switching from indole (**2d**) to its *N*-Me counterpart **2k**, it was noticed that changing the nature of the weakly coordinating counteranion from OTf^- to NTf_2^- afforded better results in this tandem process. The reaction of **1c** with **2k** in DCM at reflux indeed led to the complete consumption of the substrate and isolation of a separable mixture of two regioisomeric 6-*exo-dig* and 7-*endo-dig* cyclized products, namely benzoindolizinone **8b** and benzoazepinone **10b**, in a good 70% combined yield and with appreciable *exo* selectivity (2:1 ratio, entry 2).

As far as binucleophilic π aromatics are concerned in this tandem Friedel–Crafts/hydroarylation sequence, complete regiocontrol in the amidoalkylation step is crucial to avoid complex mixtures of products at the end of the process. *N*-TIPS-pyrrole (**2l**) was thus chosen for its ability to direct total *meta* selectivity in the Friedel–Crafts amidoalkylation reaction, a feature not shared by pyrrole (see Table 3, entry 5) or *N*-Me-pyrrole. The reaction of **2l** and **1c** under our optimized conditions gave benzoindolizinone **8c** and benzoazepinone **10c** in a modest overall yield of 30% (entry 3), which may be the consequence of extensive desilylation possibly occurring at different stages of the tandem sequence.[36] A noteworthy, intriguing, and completely reversed *endo* selectivity was noted here. Finally, 2-methylthiophene (**2m**) was also found to be a suitable partner and produced the expected products **8d** and **10d** in a synthetically useful combined yield of 65%, again with a very high *endo* selectivity (entry 4).

As far as we are aware, these are the first examples of a catalytic cascade process encompassing an intermolecular *N*-acyliminium coupling step. Although sufficiently satisfactory at this stage, the above sequence still suffers from some limitations and we are currently seeking to further optimize the reaction conditions.

Conclusion

We have found that gold(I) and gold(III) are able to efficiently catalyze the nucleophilic substitution reaction of various alkoxy- and acetoxylactams. The reaction was found to be applicable to a wide range of cyclic *N*-acyliminium ion precursors and various nucleophiles, including allyltrimethylsilane, silyl enol ethers, arenes, and active methylene derivatives. This chemistry broadens the scope of gold catalysis by highlighting new aspects of the σ-Lewis acidity of gold salts. More importantly, this approach is amenable to an expedient access to complex aza-heterocycles by way of a one-pot gold-catalyzed α-amidoalkylation/hydroarylation reaction sequence in which gold sequentially acts as Lewis acid and transition metal. Improvements in terms of efficiency and scope of the one-pot cascade process by using single and multiple catalytic systems are currently under intensive investigation and the results will be disclosed in due course.

Experimental Section

General: Commercially available compounds were used without further purification. Solvents (CH_3CN, CH_2Cl_2, $C_2H_4Cl_2$) were distilled prior to use, taking precaution to exclude moisture by heating at reflux over CaH_2. All reactions were performed under argon. All glass apparatus was oven dried and cooled under vacuum before use. TLC was performed on sheets of silica gel 60 precoated with fluorescent indicator UV_{254} (Merck). Detection was accomplished by irradiation with a UV lamp and by using an ethanolic solution of *p*-anisaldehyde. Chromatographic separations were achieved on silica gel columns (Kieselgel 60, 40–63 μm, Merck) typically using cyclohexane/ethyl acetate as eluent. In all cases, distilled solvents were used as eluents for column chromatography. Melting points were determined on a Stuart Scientific SMP 10 analyzer and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR Paragon 1000 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance™ 300 MHz spectrometer. Chemical shifts (δ) are reported in parts per million. Mass spectra (GC-MS) were obtained on a ThermoFinnigan Automass III spectrometer coupled with a gas chromatograph Trace GC 2000. HRMS were recorded on an Agilent 6530 Q-Tof MS system.

General procedure for the one-pot α-amidoalkylation/hydroarylation sequence catalyzed by gold complexes: Under an argon atmosphere, dry solvent (DCM or DCE, 0.5 mL) was added to a mixture of 2 mol% of AuCl and 2 mol% of silver salt (AgOTf or $AgNTf_2$). After stirring at room temperature for 15 min, lactam **1c** and the nucleophile (0.9–1.2 equiv) were added to the AuX (X = OTf or NTf_2) catalyst solution. Completion of the Friedel–Crafts amidoalkylation step was monitored by TLC. Then a solution of 5 mol% of $[(Ph_3P)AuNTf_2]$ in solvent (0.6 mL) was added. Once no more evolution was observed (TLC analysis), a further portion of $[(Ph_3)AuNTf_2]$ catalyst (5 mol% as a solution in 0.6 mL of solvent) was added. After complete conversion of the Friedel–Crafts intermediate, the reaction mixture was diluted with solvent, filtered through Celite, and removed under reduced pressure.

Synthesis of indole adducts 8a and 9a: The typical procedure using AuOTf for the Friedel–Crafts amidoalkylation step was applied to acetoxylactam **1c** (80 mg, 0.349 mmol, 1 equiv) and indole (**2d**; 37 mg, 0.314 mmol, 0.9 equiv) in DCE (1.75 mL) to afford the products **8a** and **9a**. The products were purified by column chromatography on silica gel by using ethyl acetate/cyclohexane (30:70) as eluent.

*6-Methylene-6,7-dihydro-5H-benzo[1,2]indolizino[7,8-b]indol-9(13bH)-one (**8a**)*: Yellow solid (44 mg, 49%), m.p. 149°C; R_f = 0.3 (ethyl acetate/cyclohexane, 50:50); ^1H NMR (300 MHz, $CDCl_3$, 20°C): δ = 8.60 (br s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 8.02 (d, J = 6.8 Hz, 1H), 7.88 (d, J = 7.5 Hz,

1H), 7.60 (t, J=7.5 Hz, 1H), 7.45 (t, J=7.5 Hz, 1H), 7.37 (m, 1H), 7.23 (m, 2H), 6.08 (s, 1H), 5.34 (s, 1H), 5.27 (d, J=14.8 Hz, 1H), 5.17 (s, 1H), 3.98 ppm (d, J=14.8 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$, 20°C): δ= 168.8 (C_q), 145.4 (C_q), 137.5 (C_q), 132.5 (CH), 132.2 (C_q), 132.1 (C_q), 128.7 (CH), 125.5 (C_q), 124.5 (2 CH), 124.4 (CH), 123.9 (C_q), 120.7 (CH), 120.2 (CH), 112.0 (CH_2), 111.8 (C_q), 107.3 (CH), 58.9 (CH), 43.6 ppm (CH_2); IR ($CHCl_3$): $\tilde{\nu}$=3022, 1685, 928, 849, 790 cm^{-1}; LRMS (EI): m/z (%): 281 (59), 222 (44), 221 (100), 207 (72), 147 (95), 73 (74); HRMS (+ESI): calcd for $C_{19}H_{15}N_2O$ $[M+H]^+$: 287.1184; found: 287.1180.

*6-Methyl-9H-benzo[1,2]indolizino[7,8-b]indol-9-one (**9a**)*: White solid (13.4 mg, 15%), m.p. 94°C; $R_{f=}$0.47 (ethyl acetate/cyclohexane, 40:60); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C): δ=8.77 (t, J=7.0 Hz, 2H), 8.60 (d, J=7.8 Hz, 1H), 8.56 (s, 1H), 8.10 (d, J=7.7 Hz, 1H), 7.88 (t, J=7.6 Hz, 1H), 7.70 (dd, J=15.8, 7.9 Hz, 2H), 7.50 (t, J=7.6 Hz, 1H), 2.86 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C): δ=159.7 (C_q), 146.0 (CH), 139.2 (C_q), 134. 8 (C_q), 133.7 (C_q), 133.6 (CH), 130.1(CH), 130.0 (C_q), 129.7 (CH), 129.3 (CH), 129.1 (C_q), 128.9 (C_q), 128.4 (C_q), 125.6 (C_q), 125.5 (CH), 123.9 (CH), 123.2 (CH), 117.6 (CH), 17.4 ppm (CH_3); IR ($CHCl_3$): $\tilde{\nu}$=3019, 1678, 1339, 755 cm^{-1}; LRMS (EI): m/z (%): 284 (71) $[M]^+$, 281 (78), 207 (89), 199 (100), 147 (79), 73 (75); HRMS (+ESI): calcd for $C_{19}H_{13}N_2O$ $[M+H]^+$: 285.1028; found: 285.1020.

Synthesis of *N*-methylindole adducts 8b and 10b: The typical procedure by using $AuNTf_2$ for the Friedel–Crafts amidoalkylation step was applied to acetoxylactam **1c** (60 mg, 0.262 mmol, 1 equiv) and 1-methylindole (**2k**; 34.3 μL, 0.275 mmol, 1.05 equiv) in DCM (1.3 mL) to afford the products **8b** and **10b**. The products were purified by column chromatography on silica gel by using ethyl acetate/cyclohexane (40:60) as eluent.

*5-Methyl-6-methylene-6,7-dihydro-5H-benzo[1,2]indolizino[7,8-b]indol-9-(13bH)-one (**8b**)*: White solid (36.5 mg, 46%), m.p. 166°C, R_f=0.38 (ethyl acetate/cyclohexane, 50:50); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C): δ=8.07 (dd, J=14.0, 7.7 Hz, 2H), 7.88 (d, J=7.5 Hz, 1H), 7.56 (dd, J= 11.0, 4.1 Hz, 1H), 7.44 (t, J=7.5 Hz, 1H), 7.35 (t, J=7.3 Hz, 2H), 7.27 (m, 1H), 6.13 (s, 1H), 5.45 (s, 1H), 5.44 (s, 1H), 5.15 (d, J=13.8 Hz, 1H), 3.92 (d, J=13.8 Hz, 1H), 3.83 ppm (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C): δ=169.3 ($C_{q,C=O}$), 146.1 (C_q), 139.2 (C_q), 133.0 (C_q), 132.3 (C_q), 132.2 (C_q), 132.0 (CH), 128.4 (CH), 124.3 (C_q), 124.2 (CH_2), 123.9 (CH), 123.2 (CH), 120.3 (CH), 119.8 (CH), 112.3 (CH), 111.2 (C_q), 110.0 (CH), 58.5 (CH), 46.6 (CH_2), 31.9 ppm (CH_3); IR ($CHCl_3$): $\tilde{\nu}$=3019, 1685, 1216, 928 cm^{-1}; HRMS (+ESI): calcd for $C_{20}H_{17}N_2O$ $[M+H]^+$: 301.1340; found: 301.1335.

*5-Methyl-8,14b-dihydroisoindolo[2',1':1,2]azepino[4,3-b]indol-10(5H)-one (**10b**)*: Yellow solid (18.9 mg, 24%), m.p. 169°C, R_f=0.27 (ethyl acetate/cyclohexane, 50:50); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C): δ=7.98 (d, J= 7.7 Hz, 1H), 7.84–7.70 (m, 2H), 7.42–7.36 (m, 2H), 7.34 (d, J=3.9 Hz, 2H), 7.29 (d, J=4.0 Hz, 1H), 6.64–6.56 (m, 2H), 6.50 (s, 1H), 4.74 (dd, J=15.2, 6.3 Hz, 1H), 3.81 (dd, J=15.1, 2.5 Hz, 1H), 3.67 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C): δ=168.6 ($C_{q,C=O}$), 146.3 (C_q), 137.6 (C_q), 132.5 (CH), 132.4 (C_q), 132.0 (C_q), 131.5 (CH), 128.3 (CH), 126.3 (C_q), 123.4 (CH), 123.0 (CH), 122.9 (CH), 121.9 (CH), 119.9 (CH), 119.2 (CH), 112.3 (C_q), 109.8 (CH), 60.7 (CH), 39.5 (CH_2), 29.7 ppm (CH_3); IR ($CHCl_3$): $\tilde{\nu}$=3019, 1601, 929, 849 cm^{-1}; HRMS (+ESI): calcd for $C_{20}H_{16}N_2ONa$ $[M+Na]^+$: 323.1159; found: 323.1155.

Synthesis of *N*-(triisopropylsilyl)pyrrole adducts 8c and 10c: The typical procedure by using $AuNTf_2$ for the Friedel–Crafts amidoalkylation step was applied to acetoxylactam **1c** (60 mg, 0.262 mmol, 1 equiv) and 1-(triisopropylsilyl)pyrrole (**2l**; 77.6 μL, 0.314 mmol, 1.2 equiv) in DCM (1.3 mL) to afford the products **8c** and **10c**. The products were purified by column chromatography on silica gel by using ethyl acetate/cyclohexane (40:60) as eluent.

*4-Methylene-3-(triisopropylsilyl)-4,5-dihydro-3H-pyrrolo[3',2':3,4]pyrido-[2,1-a]isoindol-7(11bH)-one (**8c**)*: Yellow liquid (1.4 mg, 2%), R_f=0.31 (ethyl acetate/cyclohexane, 20:80); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C): δ=7.85 (d, J=7.5 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H), 7.58 (td, J=7.5, 1.1 Hz, 1H), 7.45 (t, J=7.5 Hz, 1H), 6.92 (d, J=3.0 Hz, 1H), 6.45 (d, J= 3.0 Hz, 1H), 5.68 (s, 1H), 5.12 (s, 1H), 5.10 (s, 1H), 5.01 (d, J=14.1 Hz, 1H), 4.00 (d, J=14.0 Hz, 1H), 1.70–1.53 (m, 3H), 1.18–1.05 ppm (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C): δ=168.2 ($C_{q,C=O}$), 145.8 (C_q), 133.7 (C_q), 132.4 (C_q), 131.8 (CH), 131.2 (C_q), 129.1 (CH), 128.3 (CH), 124.0 (CH), 123.3 (C_q), 123.1 (C_q), 122.8 (CH), 108.2 (CH_2), 106.8 (CH), 58.1 (CH), 46.7 (CH_2), 18.50 (3 CH_3), 14.1 ppm (3 CH); IR ($CHCl_3$): $\tilde{\nu}$= 3018, 1681, 1221, 1208, 929 cm^{-1}; LRMS (EI): m/z (%): 356 (41), 355 (100), 281 (43), 221 (71), 207 (31), 147 (75), 73 (57); HRMS (+ESI): calcd for $C_{24}H_{33}N_2OSi$ $[M+H]^+$: 393.2362; found: 393.2323.

*3-(Triisopropylsilyl)-6,12b-dihydropyrrolo[3',2':3,4]azepino[2,1-a]isoindol-8(3H)-one (**10c**)*: Yellow liquid (28.6 mg, 28%), R_f=0.22 (ethyl acetate/cyclohexane, 20:80); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C): δ=7.83 (d, J= 7.5 Hz, 1H), 7.69 (d, J=7.6 Hz, 1H), 7.56 (t, J=7.3 Hz, 1H), 7.45 (t, J= 7.5 Hz, 1H), 6.81 (d, J=2.8 Hz, 1H), 6.60 (d, J=11.0 Hz, 1H), 6.33 (d, J=2.7 Hz, 1H), 5.97 (dt, J=11.1, 5.8 Hz, 1H), 5.68 (s, 1H), 4.42 (dd, J= 16.1, 5.9 Hz, 1H), 4.13 (dd, J=16.0, 5.2 Hz, 1H), 1.60–1.39 (m, 3H), 1.17–0.99 ppm (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C): δ=167.7 ($Cq_{,C=O}$), 144.9 (C_q), 133.0 (C_q), 132.2 (C_q), 131.3 (CH), 129.4 (C_q), 128.9 (C_q), 128.2 (CH), 126.6 (CH), 125.7 (CH), 123.8 (CH), 123.7 (C_q), 123.4 (CH), 123.1 (CH), 109.5 (CH), 60.2 (CH), 41.1 (CH_2), 18.3 (3 CH_3), 13.2 ppm (3 CH); IR ($CHCl_3$): $\tilde{\nu}$=3017, 1681, 1224, 929, 849 cm^{-1}; HRMS (+ESI): calcd for $C_{24}H_{33}N_2OSi$ $[M+H]^+$: 393.2362; found: 393.2350.

Synthesis of 2-nethylthiophene adducts 8d and 10d: The typical procedure with $AuNTf_2$ for the Friedel–Crafts amidoalkylation step was applied to acetoxylactam **1c** (60 mg, 0.262 mmol, 1 equiv) and 2-methylthiophene (**2m**; 30.3 μL, 0.314 mmol, 1.2 equiv) in DCM (1.3 mL) to afford the products **8d** and **10d**. The products were purified by column chromatography on silica gel by using ethyl acetate/cyclohexane (40:60) as eluent.

*2-Methyl-4-methylene-4,5-dihydrothieno[2',3':3,4]pyrido[2,1-a]isoindol-7-(11bH)-one (**8d**)*: Yellow solid (1.4 mg, 2%), R_f=0.47 (ethyl acetate/cyclohexane, 40:60); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C): δ=7.86 (d, J= 7.8 Hz, 1H), 7.74 (d, J=7.8 Hz, 1H), 7.62 (t, J=7.5 Hz, 1H), 7.51 (t, J= 7.4 Hz, 1H), 6.84 (m, 1H), 5.75 (s, 1H), 5.32 (s, 1H), 5.17 (d, J=15.6 Hz, 1H), 5.12 (s, 1H), 4.02 (d, J=15.6 Hz, 1H), 2.45 ppm (s, 3H); IR ($CHCl_3$): $\tilde{\nu}$=3018, 1602, 1226, 929 cm^{-1}; HRMS (+ESI): calcd for $C_{16}H_{14}NOS$ $[M+H]^+$: 268.0795; found: 268.0790.

*2-Methyl-6H-thieno[3',2':3,4]azepino[2,1-a]isoindol-8(12bH)-one (**10d**)*: Yellow solid (44.1 mg, 63%), m.p. 119°C, R_f=0.40 (ethyl acetate/cyclohexane, 50:50); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C): δ=7.82 (d, J= 7.6 Hz, 1H), 7.64 (d, J=7.6 Hz, 1H), 7.56 (t, J=7.4 Hz, 1H), 7.46 (t, J= 7.3 Hz, 1H), 6.91 (s, 1H), 6.38 (dd, J=10.9, 2.1 Hz, 1H), 6.08 (m, 1H), 5.83 (s, 1H), 4.75 (dd, J=16.8, 6.2 Hz, 1H), 3.99 ppm (ddd, J=16.7, 3.7, 2.3 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C): δ=167.3 ($C_{q,C=O}$), 143.6 (C_q), 139.9, (C_q), 135.2 (CH), 133.6 (CH), 131.9 (CH), 131.4 (C_q), 128.3 (CH), 126.1 (CH), 125.8 (CH), 124.1 (CH), 123.6 (C_q), 122.9 (C_q), 62.7 (C_q), 41.1 (CH_2), 15.2 ppm (CH_3); IR ($CHCl_3$): $\tilde{\nu}$=3019, 1685, 929, 909 cm^{-1}; HRMS (+ESI): calcd for $C_{16}H_{14}NOS$ $[M+H]^+$: 268.0795; found: 268.0785.

Acknowledgements

Financial support provided by the region of Haute-Normandie is gratefully acknowledged.

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Received: June 22, 2012
Revised: July 27, 2012
Published online: September 20, 2012

