Rediscovering copper-based catalysts for intramolecular carbon–hydrogen bond functionalization by carbene insertion†

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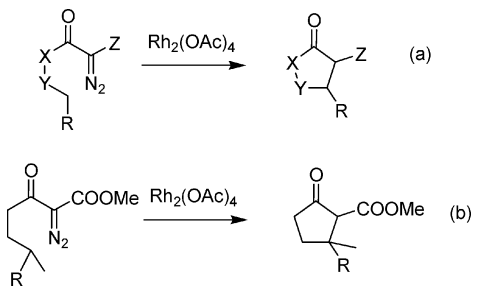
A series of Tp^xCu complexes (Tp^x = hydrotrispyrazolylborate ligand) have been tested as catalysts for the decomposition of several diazoacetates and *N*,*N*-disubstituted diazoacetamides and the subsequent formation of lactones and lactams, respectively. The complexes containing the ligands Tp^{Br3} or Tp^{Ms} have provided activities and selectivities for these transformations comparable with or, in some cases, better than the well-known rhodium catalyst $Rh_2(OAc)_4$.

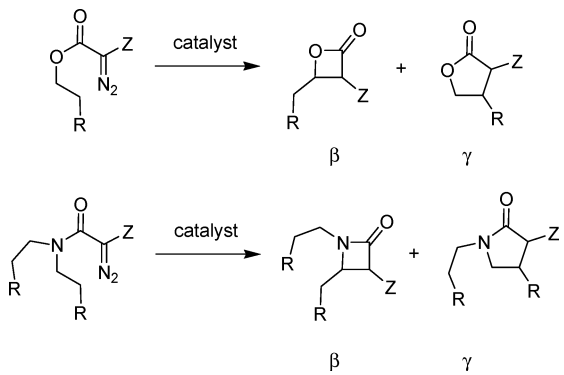
Introduction

The intramolecular insertion of a metal-induced, in situ-generated carbene fragment into a C–H bond constitutes a useful strategy to construct cyclic compounds (Scheme 1, a).[1] The first examples were described using simple copper salts as the catalyst, but had low yields and a reduced scope.[2] In the mid 80s, the groups of Wenkert[3] and Taber[4] independently described the catalytic capabilities of $Rh_2(OAc)_4$ towards the intramolecular diazoketone decomposition and subsequent cyclopentanone formation by C–H insertion (Scheme 1, b).



Scheme 1 Intramolecular carbenoid carbon–hydrogen insertion reactions.

A particular case of the above transformations is based on the use of diazoacetates or diazoacetamides which would lead to the formation of lactones and lactams respectively (Scheme 2). Both reactions have been developed with rhodium-based catalysts,[5] whereas the use of copper has been scarcely reported.[1,6] Doyle and co-workers have provided a series of excellent contributions in this area, where rhodium carboxylate and rhodium carboxamide complexes were described as very efficient catalysts for the formation of γ-lactones.[7] The same or related catalysts were also reported by Doyle *et al.* for the decomposition of α-diazoacetamides and the subsequent formation of lactams.[8] In recent years, Afonso and co-workers[9] have developed environmentally friendly systems using ionic liquids as reaction media, based on rhodium, for the latter transformation. It is worth mentioning an exception in this rhodium-controlled area: Maas and co-workers[10] have recently described a catalytic system using diruthenium(I,I) catalysts for the synthesis of β- and γ-lactams from α-diazoacetamides on the gram scale.



Scheme 2 Synthesis of lactones (top) and lactams (bottom) by intramolecular C–H insertion of diazocompounds.

During this decade, our group has been focused on the development of group 11 metal-based catalysts for intermolecular C–H functionalization reactions,[11] including carbene insertion reactions from diazocompounds. Copper complexes containing hydrotrispyrazolylborate ligands (Tp^x) have been found to efficiently promote the insertion of $:CHCO_2Et$ units into the C–H bonds of alkanes or cyclic ethers, among others.[12] On the basis of this background, and the limited number of examples of lactone and lactam syntheses based on intramolecular C–H insertion methodology, we decided to investigate the potential of our well known Tp^xCu catalysts for the latter transformations.

Results and discussion

Synthesis of lactones mediated by Tp^xCu complexes

The formation of lactones was screened using isopropyl- and *tert*-butyl diazoacetate as reagents and four copper complexes (**1–4**, Scheme 3), containing different Tp^x ligands, as catalysts. A dichloromethane solution containing the diazocompound

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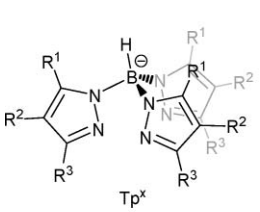
† Electronic supplementary information (ESI) available: Experimental details, characterization data and NMR spectra of the reaction products. See DOI: 10.1039/b911589g

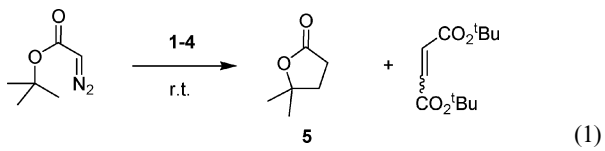


R^1	R^2	R^3	Tp^x	Tp^xCu
Me	H	Me	Tp^*	**1**
H	Br	C_6H_{11}	$Tp^{Cy,4Br}$	**2**
Br	Br	Br	Tp^{Br3}	**3**
H	H	Ms	Tp^{Ms}	**4**

Scheme 3 Ligands and catalysts employed in this work.

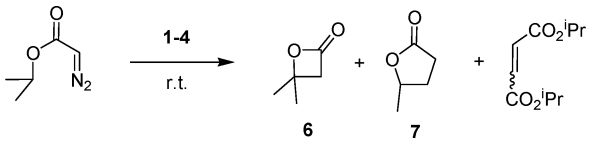
(1 mmol) was slowly added into a flask containing a dichloromethane solution with 0.0125 mmol of the copper complex, with the aid of a syringe pump (addition time = 6 h).

At the end of the addition, IR studies of the reaction mixture revealed the complete consumption of the diazo reagent. NMR studies revealed the presence in the final mixture of the γ-lactone **5**, along with the products derived from the coupling of two carbene units (eqn 1). Although already reported for these transformations, we have also carried out, for the sake of comparison, the same experiments in the presence of $Rh_2(OAc)_4$ under identical reaction conditions. Data in Table 1 shows that the capabilities of the four complexes **1–4** to induce the formation of **5** are quite distinct, ranging from nearly null (**1**) to almost quantitative (**4**).



5 (1)

At variance with *tert*-butyl diazoacetate, the use of the isopropyl analogue can provide, in principle, two different products depending on the reaction site (eqn 2). Thus, the insertion of the carbene group into the tertiary C–H bond would afford the β-lactone **6** whereas if such insertion occurred in the primary C–H bond, the formation of the γ-lactone **7** would take place. When complexes **1–4** where employed as catalysts for this reaction, mixtures of both compounds were observed. However, high regioselectivity was induced by catalyst **4**, that gave a 87:5 mixture of **6**:**7**, respectively, and only 8% of coupling products, with quantitative conversion of the diazocompound after 6 h of reaction time. Under the same conditions, the polybrominated $Tp^{Br3}Cu$ catalyst also gave a large amount of the four-membered ring **6** (71:11). It is worth mentioning that ethyl diazoacetate (EDA) also underwent the intramolecular activation of the C–H bonds, although to a lesser extent, to give the β-lactone, and only with catalyst **3** and **4**. Complexes **1** and **2**, as well as rhodium acetate, induced the complete conversion of EDA into diethyl fumarate and maleate. The effect of the structure of the catalyst in the reaction profile will be discussed below.



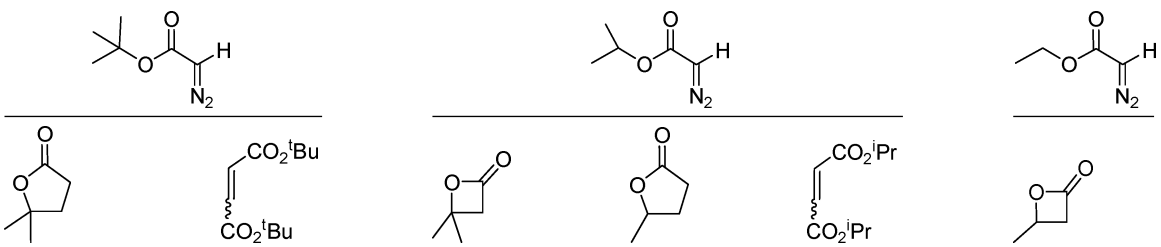
6 **7** (2)

Preparative experiments were carried out with both diazocompounds at the 2 mmol scale, with a 1.25% catalyst loading, and a 12 h reaction time. Under these reaction conditions, exclusive formation of **5** and **6** was observed (99% isolated yields of both products).

Synthesis of lactams by intramolecular C–H insertion induced by Tp^xCu complexes

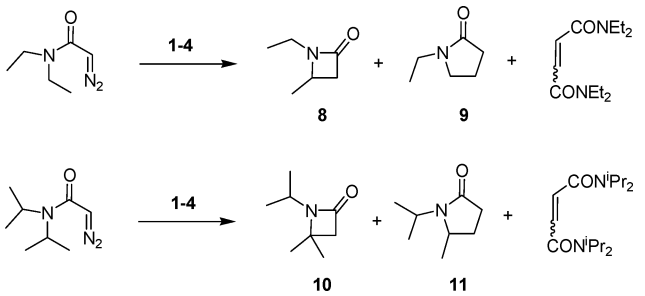
Once the potential of the Tp^xCu complexes had been established, and particularly that of complexes **3–4**, for the formation of lactones from diazocompounds, we decided to extend the study to the effect of such complexes for the related reaction that employs α-diazoacetamides as reagents. Following a similar procedure (see Experimental Section), the complexes **1–4** were used in catalytic amounts with *N*,*N*-diethyl- and *N*,*N*-diisopropyldiazoacetamide as the substrates. In both cases, mixtures of the corresponding β- and γ-lactams were obtained in variable yields depending on the catalyst employed (Scheme 4). The less sterically hindered *N*,*N*-diethyldiazoacetamide was preferentially converted into the γ-lactam **9** in all cases, the best conversions being obtained

Table 1 Synthesis of lactones from diazocompounds using Tp^xCu complexes as catalysts[a]



Catalyst						
1	4	96	3	7	90	0
2	35	65	np[b]	np[b]	np[b]	0
3	81	9	71	11	18	22
4	98	2	87	5	8	17
4[c]	99[c]	nd	99[c]	nd	nd	13[c]
$Rh_2(OAc)_4$	87	13	40	15	45	0

[a] Catalyst loading: 1.25% with respect to 1 mmol of the diazoacetate. Addition time of the diazocompound from syringe pump: 6 h. Conversions measured with internal standard. [b] np = not performed. [c] Preparative scale experiment: 2 mmol of diazocompound, 1.25% catalyst loading, slow addition for 12 h, isolated yield.



Scheme 4 Synthesis of lactams by intramolecular C–H insertion induced by complexes **1–4**.

with catalyst $Tp^{Br3}Cu$ (**3**) under slow diazocompound addition conditions; only 3% of the coupling products were observed, in contrast with the large amount of such byproducts obtained with **1** under the same conditions (Table 2). In the case of catalyst $Tp^{Ms}Cu$ (**4**), no reaction was observed at room temperature, with most of the diazocompound being recovered after 12 h of stirring. However, upon heating for the same period at 70 °C, 88% conversion was obtained, a 41:47 mixture of **8**:**9** being detected. In order to ascertain if this ratio, somewhat anomalous if compared not only with the other copper catalysts but also with rhodium acetate, was formed due to the temperature raise, we repeated the reaction at 70 °C with catalyst $Tp^{Br3}Cu$ (**3**). The selectivity was quite similar to that developed at room temperature, so the nearly 1:1 ratio obtained with catalyst **4** is due to the catalyst nature. It is worth mentioning that this reaction is sensitive toward the catalyst:diazocompound ratio in solution, since the use of slow addition devices clearly improved the yields of the desired products.

The use of *N*,*N*-diisopropyldiazoacetamide has also provided interesting results (Table 2). At room temperature, and with the diazocompound added in one portion, catalyst **3** induced the complete conversion into lactams **10** and **11**, with no coupling products being detected. In this case, the regioselectivity favored the formation of the β-lactam **10**, to give a 87:13 mixture of **10**:**11**. Catalysts **2** and **4** also afforded high conversions into the products, the latter again at 70 °C, with selectivities similar to that observed with **3**, only **2** yielding considerable amounts of the non-desired coupling products.

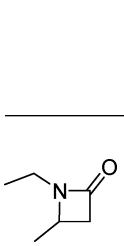
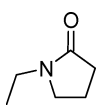
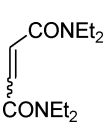
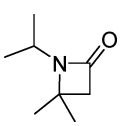
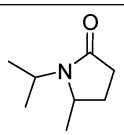
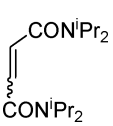
The copper–rhodium comparison

As mentioned above, dirhodium tetraacetate has been widely employed for these transformations. We have now found that the trispyrazolylborate complexes of copper(I) can induce the decomposition of the model diazocompounds employed in this work and the subsequent C–H bond functionalization by means of an intramolecular carbene insertion pathway. A closer look to the data contained in Tables 1 and 2 provides some interesting information regarding the capabilities of such copper catalysts in comparison with the rhodium counterpart. It is worth mentioning that control experiments using $Rh_2(OAc)_4$ have been run under the same conditions in order to assess an unambiguous comparison between both systems. Catalyst loading was fixed at 1.25% relative to the diazocompound, with reactions carried out at room temperature (unless otherwise noted), and the same concentrations of reactants in all the experiments.

In the case of the formation of lactones, the $Tp^{Ms}Cu$ catalyst (**4**) displayed an excellent catalytic activity that surpassed those observed with rhodium acetate. Thus, the five-member lactone **5** was obtained in 98% yield under the same conditions that gave 87% using $Rh_2(OAc)_4$. Similarly, with isopropyl diazoacetate as the diazocompound, a 92% yield of a 87:5 mixture of the β- and γ-lactams was obtained, whereas the rhodium catalyst only gave a 60% yield (2:1 ratio for β:γ). This value could be improved by extending the addition time to 12 h to give quantitative conversion into lactone **5** (Table 1).

This catalytic system also delivered good results when applied to diazoacetamides, the perbrominated catalyst $Tp^{Br3}Cu$ (**3**) providing the best conversions and selectivities at room temperature. For *N*,*N*-diethyldiazoacetamide as the substrate, and adding the diazocompound in one portion at the beginning of the reaction (1 h overall reaction time), catalyst **3** gave a 82% yield of a mixture of **8** and **9** (21:61, respectively), whereas under the same conditions $Rh_2(OAc)_4$ gave a 69% yield, with a 6:63 **8**:**9** ratio. The amount of the coupling products can be diminished by

Table 2 Synthesis of lactams from diazocompounds using Tp^xCu complexes as catalysts[a]

Catalyst						
1	4(18)	6(23)	90(59)	48	15	37
2	17(30)	20(33)	73(37)	84	14	2
3	21(26)	61(71)	18(3)	87	13	nd
3[b]	20	51	17	81	6	0
4[c]	41	47	12	82	15	3
$Rh_2(OAc)_4$	6	63	31	66	27	7

[a] Catalyst loading: 1.25% with respect to 1 mmol of the diazoacetamide. All the reactions were carried out by adding the diazoacetamide in one portion at the beginning of the reaction. Values in brackets are for experiments using a syringe pump and 3 h of slow addition. [b] Isolated yields. [c] At 70 °C.

using slow addition techniques. In contrast, the use of *N*,*N*-diisopropyldiazoacetamide as the reactant did not require the use of such a device, the reagent could be added in one sole portion. Again, complex **3** gave the highest chemoselectivity, >99%, with no coupling products being detected at the NMR detection limit. The β-lactam **10** was the major product with any catalyst, complex **3** yielding an 87:13 mixture of **10**:**11**, respectively, with just 1 h of stirring. Such conversion and selectivity were similar to those obtained with $Tp^{Cy,4Br}Cu$ (**2**) and $Tp^{Ms}Cu$ (**4**), although the latter was employed at 70 °C. The rhodium catalyst provided slightly lower conversions (93%) and a lower regioselectivity (66:27 for **10**:**11**) than $Tp^{Br3}Cu$ under identical experimental conditions.

An important issue in this chemistry is the negative effect of the presence of adventitious water in the reaction mixture. We have found that in this case, and in good accord with previous observation of intermolecular catalytic systems,[12] the insertion of the carbene species into the O–H bond of water may occur, *both with the copper as well as with the rhodium catalysts*. Actually, recent work by Afonso and co-workers has taken advantage of this behavior for synthetic purposes.[9e] Therefore, precaution must be taken to avoid this side reaction. The second issue to be discussed is the need for an inert atmosphere when using a Cu(I) complex as the catalyst. We have recently shown that the reactivity of the Tp^xCu complexes toward molecular oxygen in solution depends on the Tp^x ligand,[13] the reactivity being diminished when the electron density at the metal center is decreased. Complexes **1** and **2** fall in the range of those that readily react with oxygen, and therefore, an inert atmosphere is required to maintain their oxidation state as +1. However, complexes **3** and **4** do not react readily with oxygen in solution, and catalysis can be performed in open air, as in the case of $Rh_2(OAc)_4$. Unfortunately, this is only the case if the air is completely dry, otherwise the side reaction with water would take place. Because of this, we have performed the experiments under a nitrogen atmosphere; under air, carbene transfer takes place but insertion into O–H bonds diminished the yields of the desired compounds.

Catalyst activities and selectivities

The general, well-known trend for reactivity of carbon–hydrogen bonds for this insertion process is tertiary>secondary>primary.[14] In addition, the vicinal-to-heteroatom positions are favored due to a lower C–H bond dissociation energy of such bonds.[15] On the basis of this, the trends shown in Tables 1 and 2 for each catalyst when varying the diazocompounds are readily explained. In the case of lactone formation, the use of the isopropyl diazoacetate may lead to four- (**6**) and five-membered (**7**) cycles derived from the insertion into the tertiary or primary C–H sites. In spite of the recognized thermodynamic stability of five-membered rings, the reaction takes place favoring the formation of the β-lactone **6**, where the more reactive tertiary site, also vicinal to the oxygen atom, is functionalized. The same trend is observed for *N*,*N*-diisopropyldiazoacetamide (Table 2).

When X-ethyl (X = O, N) substituted diazo compounds N_2=CH–COX were employed, a distinct behavior was observed. For ethyl diazoacetate, the expected β-lactone was observed, although in low yields since diethyl fumarate and maleate were the major products. Actually, this lactone is not observed with dirhodium tetraacetate. *N*,*N*-Diethyldiazoacetamide was preferentially converted into the γ-lactam with the series of copper-based catalysts, as well as with $Rh_2(OAc)_4$. This is a case in which a primary site is preferred over a secondary, vicinal to nitrogen, site. The same behavior has been previously described with rhodium and ruthenium catalysts.[7–10] We do not have, at the present stage, a detailed explanation for this general, non-catalyst dependent, observation.

As inferred from data in Tables 1 and 2, the four copper catalysts **1**–**4**, for a given substrate, can be divided into two groups, according to the activity shown. Complexes **1** and **2** induce low conversions into the desired products, with large amounts of the coupling byproducts being formed. On the other hand, the Tp^{Br3}- and Tp^{Ms}-containing catalysts provided very good yields of lactones and lactams, comparable, or superior in some cases, to those obtained with $Rh_2(OAc)_4$ under the same conditions. It is well established that the functionalization of C–H bonds by carbene insertion requires an electrophilic metal center. We have already described[13] the trend of electron density at the metal center in complexes Tp^xCu on the basis of IR studies of the corresponding $Tp^xCu(CO)$. For the complexes employed in this work, the array of ν(CO) is 2056 (Tp*), 2068 ($Tp^{Cy,4Br}$), 2079 (Tp^{Ms}) and 2107 (Tp^{Br3}) cm^{-1}, which follows the trend in yields in the insertion products for the substrates in Tables 1 and 2. The observation of higher yields in the case of Tp^{Ms} could be explained in terms of a higher protection of the transient metallocarbene intermediate with this ligand in comparison with Tp^{Br3}, since it has been proposed that this condition is required to minimize the formation of the coupling products. This difference in size of the Tp^x ligand would also affect the regioselectivity, when more than one reaction site is available. Thus, with isopropyl diazoacetate as the substrate, the amount of the β-lactone **6** obtained is increased when moving from catalyst **3** to **4**, as the result of a more reduced catalytic pocket in the case of the latter that would favor the formation of the smaller ring. However, if the reaction rate is fast, the reaction is mainly governed by the nature of the substrate, the structure of the catalyst inferring only secondary effects. This is the case when using *N*,*N*-diisopropyldiazoacetamide, for which the relative ratio of β:γ lactams is nearly identical, within experimental ratio, for catalysts **2**–**4**. For the less reactive *N*,*N*-diethyldiazoacetamide a certain degree of discrimination by the Tp^xCu catalyst is observed, and again the most sterically hindered Tp^{Ms} ligand induces an enhancement in the yield of the β-lactam.

Conclusions

We have found that complexes of general formulae Tp^xCu catalyze the functionalization of C–H bonds by means of an intramolecular carbene insertion process, which afford lactones or lactams. The activities of the catalysts containing the ligands Tp^{Br3} or Tp^{Ms} are, at least, comparable with, or in some cases better than, those obtained with $Rh_2(OAc)_4$, and do not need to work under anaerobic conditions, although the complete absence of water is required (similarly to other reported systems). These findings allow the reconsideration of the use of copper-based catalysts for these transformations, for which more active or selective catalysts, including chiral ones, can be designed in the near future.

Experimental section

General methods

All manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques. Ethyl diazoacetate and *tert*-butyl diazoacetate were purchased and employed without further purification. The complexes $[Tp^xCu]$[12,13] and diazocompounds[16] were prepared according to literature procedures. Reagents and solvents were dried and degassed before use. NMR spectra were recorded on a 400 MHz spectrometer (^{13}C NMR at 100 MHz) using $CDCl_3$ as the solvent.

General catalytic procedure for the C–H intramolecular carbene insertion from diazocompounds

A solution of the corresponding diazocompound (1 mmol) in 20 mL of CH_2Cl_2 was added either in one portion or with the aid of a syringe pump over the desired time to a solution of Tp^xCu (0.0125 mmol) in 20 mL of CH_2Cl_2. After addition, the consumption of the diazocompound (diazoacetates or diazocetamides) was monitored by IR. When no diazo was observed, volatiles were removed under vacuum and the reaction crude was analyzed by ^1H NMR spectroscopy. All the products have been previously described and their identification was straightforward from comparison with the data reported. Conversions were determined by ^1H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard. Isolated yields of representative examples were obtained upon purification of products by column chromatography with neutral silica gel or basic alumina following previously described procedures.[8b,10,17,18,19]

5,5-Dimethyl-dihydrofuran-2-one (5). ^1H NMR (400 MHz, $CDCl_3$) δ 2.6 (t, $J = 8.3$ Hz, 2H), 2.0 (t, $J = 8.3$, Hz, 2H), 1.4 (s, 1H). Data are in agreement with those reported in the literature.[17]

4,4-Dimethyloxetan-2-one (6). ^1H NMR (400 MHz, $CDCl_3$) δ 3.18 (s, 2H), 1.52 (s, 6H). Data are in agreement with those reported in the literature.[18]

5-Methyl-dihydrofuran-2-one (7). ^1H NMR (400 MHz, $CDCl_3$) δ 4.6 (tq, $J = 7.8$, 6.2 Hz, 1H), 2.6–2.5 (m, 2H), 2.5–2.3 (m, 1H), 1.9–1.7 (m, 1H), 1.4 (d, $J = 6.2$ Hz, 3H). Data are in agreement with those reported in the literature.[17]

1-Ethyl-4-methylazetidin-2-one (8). ^1H NMR (400 MHz, $CDCl_3$) δ 3.56 (m, 1H), 3.33 (m, $J = 2$H), 2.95 (m, 1H), 2.88 (dd, $J = 14.3$, 4.8 Hz, 1H), 2.35 (dd, $J = 14.3$, 2.1 Hz, 1H), 1.23 (d, $J = 6.1$ Hz, 3H), 1.1 (t, $J = 7.2$ Hz, 3H). Data are in agreement with those reported in the literature.[19]

1-Ethylpyrrolidin-2-one (9). ^1H NMR (400 MHz, $CDCl_3$) δ 3.32 (m, 2H), 3.25 (q, $J = 7.6$ Hz, 2H), 2.31 (t, $J = 8.2$ Hz, 2H), 1.95 (m, 2H), 1.05 (t, $J = 7.4$ Hz, 3H). Data are in agreement with those reported in the literature.[10]

1-Isopropyl-4,4-dimethylazetidin-2-one (10). ^1H NMR (400 MHz, $CDCl_3$) δ 3.58 (hept, J = 6.4 Hz, 1H), 2.66 (s, 2H), 1.41 (s, 6H), 1.31 (d, J = 6.9 Hz, 6H). Data are in agreement with those reported in the literature.[8b]

1-Isopropyl-5-methylpyrrolidin-2-one (11). ^1H NMR (400 MHz, $CDCl_3$) δ 4.22–4.10 (m, 1H), 4.09–4.00 (m, 1H), 2.52–2.35 (m, 2H), 2.15–2.03 (m, 2H), 1.26–1.15 (9H). Data are in agreement with those reported in the literature.[8b]

Acknowledgements

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