Lanthanum-Catalyzed Enantioselective Trifluoromethylation using Electrophilic Hypervalent Iodine Reagent

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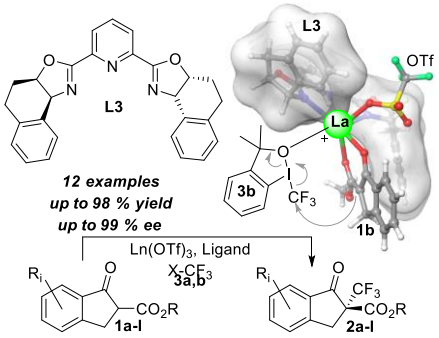
Supporting Information Placeholder



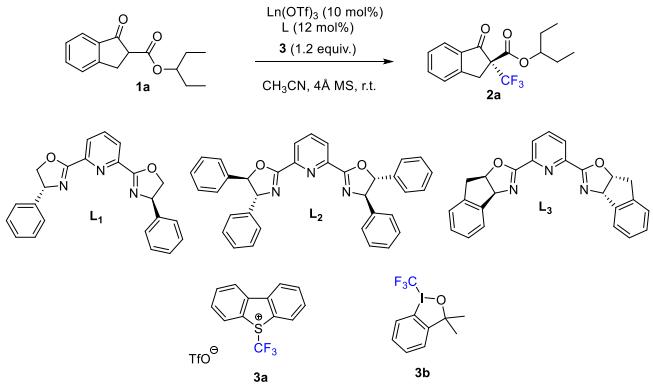
ABSTRACT: A highly enantioselective catalytic method for the synthesis of quaternary α-trifluoromethyl derivatives of 3-oxo esters is described. The reaction uses lanthanum (III) triflate and chiral pybox-type C_2-symmetric ligands to generate intermediate La(III) complexes that incorporate an enolate moiety of the starting 3-oxo ester and the trifluoromethyl transfer reagent. The enantioselectivity of the reaction stems from the efficient blockage of one of the prochiral faces of the La(III) enolate by one unit of the C_2-symmetric ligand.

Fluorinated organic compounds are extremely appealing in the course of pharmaceuticals and agrochemicals discovery.[1-5] Indeed, the appropriate introduction of a fluorine atom or a fluorinated group can drastically affect the biological and physical properties of a molecule and its physiological behavior with respect to the mode of action and metabolism.[6-9] In this context, the trifluoromethyl motif has generated high interest.[10-23] The introduction of a trifluoromethyl group in an enantioselective manner is one of the most challenging synthetic problems.[19-23] Thus, the non-asymmetric electrophilic α-trifluoromethylation of β-keto esters has been extensively studied, whereas the asymmetric examples are scarcely documented. In particular, MacMillan and co-workers reported that combining chiral organocatalysis and Lewis acid catalysis and Togni's reagent (**3b**) as a CF_3-transfer highly enantioenriched α-trifluoromethylated aldehydes could be obtained.[20] We were stimulated by the impressive work of Gade and co-workers in 2012.[23] They developed boxmi chiral pincer ligands which combined with copper proved to be excellent catalysts for the enantioselective trifluoromethylation of β-keto esters by using commercial electrophilic trifluoromethylating agents.

In our own research, we have extensively used the combination of py-box ligands and lanthanides for the enantioselective α-amination of β-keto esters.[24-27] With these precedents, we planned to use cheap commercially available py-box chiral ligands. As a first stage, we decided to test the efficiency of the catalytic system in the model reaction of β-keto ester **1a** (Scheme 1). The selection of pentan-3-yl derivative was done based in our previous findings; normally increasing the size of the ester group the enantiodifferentiation is enhanced.[25,26] Keto ester **1a** was achieved by treatment of methyl analog **1b** with the corresponding alcohol using catalytic amounts of ZnO in refluxing toluene in 89% yield.[28] The pre-catalyst was prepared mixing 10% of $Ln(OTf)_3$ and 15% of py-box ligand (**L**) in dry acetonitrile in the presence of molecular sieves during one night. Then, the β-keto ester **1a** (1 equiv.) and the trifluoromethylating transfer agent **3a-b** (1.2 equiv.) were added at room temperature. The reaction conditions

had been previously optimized for α-amination reactions.[25-27]

Initially, by using 5-(trifluoromethyl)dibenzothiophenium tetrafluoroborate **3a** (Umemoto's reagent) as the trifluoromethylating reagent, La(OTf)$_3$ and **L1**, the corresponding product **2a** was obtained in 10% yield and 50% *ee* (table 1, entry 1). Changing to Togni's reagent **3b**, product **2b** was afforded in high yield (85%), although the *ee* did not enhance (Table 1, entry 3). Screening of two other Nishiyama's type py-box ligands (**L2** and **L3**) revealed the greater effectiveness of indanyl-py-box ligand (**L3**) in obtaining an optimum reactivity and enantioselectivity that could be improved up to 91% performing the reaction at -35ºC (Table 3, entry 6). Eu(OTf)$_3$ gave less *ee* and yield, showing the dependence of the reaction with the ionic radio of the Lewis acid and selected py-box.

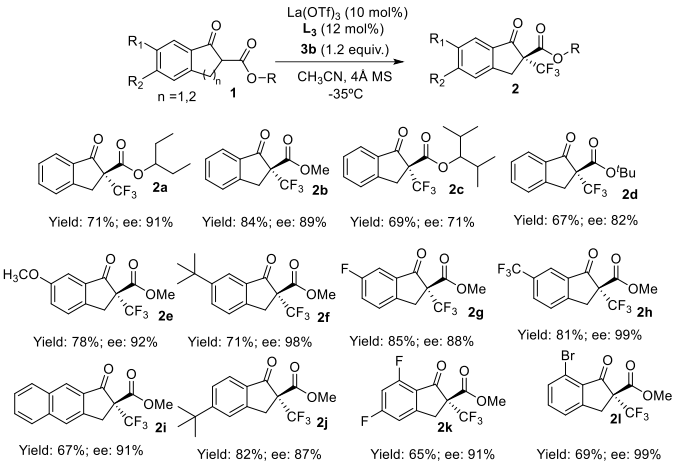


Scheme 1. Trifluoromethylation of ester 1a with La(OTf)$_3$ and reagents 3a,b in the presence of chiral ligands L1-3.

Table 1. Trifluoromethylation of β-keto ester 1a with lanthanide(III) triflates Ln(OTf)$_3$ and reagents **3a,b** in the presence of chiral basic ligands **L1-3**.

Entry	**3**	Ln	**L**	T (ºC)	Yied (%)[a]	*ee* (%)[b]
1	**3a**	La	**L1**	r.t.	10	50
2	**3a**	La	**L1**[c]	r.t.	85	15
3	**3b**	La	**L1**	r.t.	85	55
4	**3b**	La	**L2**	r.t.	82	58
5	**3b**	La	**L3**	r.t.	87	78
6	**3b**	La	**L3**	-35	71	91
7	**3b**	Eu	**L3**	-35	65	80

[a]Yields of isolated pure product **2a**. [b]Enantiomeric excesses determined by HPLC and calculated as *ee*=100 x ([R]-[S]) / ([R]+[S]). [c]DIPEA was used as a base.



Scheme 2. Synthesis of chiral esters **2a-m** with La(OTf)$_3$ and **3b** in the presence of chiral ligand **L3**.

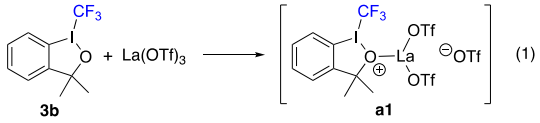
Then, a broad range of cyclic β-keto esters was examined using the optimized pre-catalyst combination and reaction conditions. Keto esters **1c,d** were prepared in high yields (68 and 85% respectively) by transesterification of the commercial methyl ester **1b** with the corresponding alcohol using catalytic amounts of ZnO in refluxing toluene.[28] First, we noticed that the size of the ester group had a strong influence on the enantiocontrol. Bulky *tert*-butyl and 2,4-dimethylpentan-3-yl esters gave lower *ee*'s (82 and 71% *ee* respectively). In contrast, indanone-derived methyl β-keto ester (**1b**) yielded the corresponding product **2b** in high enantioselectivity (89% *ee*) comparable with the pentan-3-yl derivative. This is a remarkable point since it allows applying this chemistry to simple methyl β-keto esters. Next, we studied the influence of aromatic substituents at the six-position of the aromatic part. Compounds **1e, 1g-h** and **1j-m** are commercially available, whereas **1f** was synthesized from 3-(*tert*-butylphenyl)propanoic acid using polyphosphoric acid as catalyst (ca. 100% yield).[29] No clear electronic effects were observed. Thus, in the presence of either electron–donating *tert*-butyl or electron–withdrawing trifluoromethyl groups excellent enantioselectivities were obtained. However, the ee's depend on the size of the substituent in this six-position of the aromatic ring. Large *tert*-butyl and trifluoromethyl substituents gave higher enantioselectivites (98-99%) compared with H, F and O-CH$_3$ (88-92%). Unexpectedly, a *tert*-butyl group placed in five-position rendered **2j** in a slightly lower 87% *ee*. Moreover, β-keto ester **1i** was prepared in 71% yield through a [4+2] cycloaddition of α,α,α′,α′-tetrabromo-*o*-xylene and 2-cyclopenten-1-one as previously described[30] and it's α-trifluoromethylation reaction gave an excellent 91% *ee*. Fortunately, the method can be successfully employed in the presence of substituents in other aromatic positions of the substrate. Excellent results were obtained in terms of enantioselectivity for **2k** and **2l** (91 and 99% *ee* respectively).

The assignment of the absolute configuration of **2a** as *R* was based on the comparison of the positive specific rotation described for (*S*)-**2a** in the literature.[22] Cahard also described a positive Cotton effect for the n-p transition at about 320 nm in the case of (*S*)-**2a.** As expected, this

latter compound presented a negative Cotton Effect.[22] We assigned the absolute configuration *R* to all compounds **2** showing negative specific rotation and negative Cotton effect (see Supporting Information).

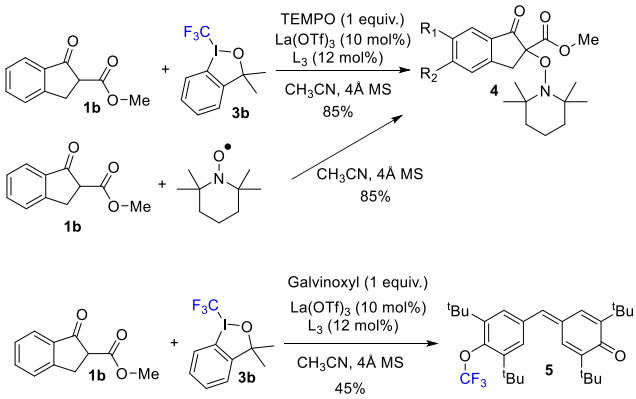
The mechanism of the reaction was first investigated by ESI-MS. We conducted an ESI mass spectrometry study to detect short-lived reaction intermediates present in the solution. Our investigation was based on the reaction of **1b** with **3b** using the combination of $La(OTf)_3$ and **L3** as a pre-catalytic system in acetonitrile at room temperature. First of all, individual components of the reaction were analyzed, as well as mixtures of two or more components and finally the ongoing reaction in its initial state and after 10 and 75 minutes, respectively (see Supporting Information). We first analyzed the binary mixtures. The ESI-MS spectrum of a stoichiometric mixture of **L3** and $La(OTf)_3$ showed one peak m/z = 829.9587 corresponding to a complex (denoted as **INT1** in Fig.1, vide infra) of lanthanium with one pybox ligand $[(\mathbf{L3})La(OTf)_2]^+$ and another peak m/z = 1223.1038 corresponding to a complex of lanthanum with two pybox ligands $[(\mathbf{L3})_2La(OTf)_2]^+$. For the mixture of **1b** with $La(OTf)_3$ we identified two peaks m/z = 626.8734 corresponding to $[(\mathbf{1b})La(OTf)_2]^+$ and m/z = 816.9357 identified as $[(\mathbf{1b})_2La(OTf)_2]^+$. No binary species could be identified from the ESI-MS spectrum of a stoichiometric mixture of Togni's reagent **3b** and $La(OTf)_3$. Then we studied ternary mixtures. From the mixture $La(OTf)_3$, **L3** and **1b** (0.4:0.4:1), we identified two important species corresponding to peaks at m/z = 870.0622 ([(enolate-**1b**)(**L3**)La(OTf)]$^+$, denoted as **INT2** in Fig. 1, vide infra) and m/z = 1263.2087 ([(enolate-**1b**)(**L3**)$_2$La(OTf)]$^+$). These results indicate that in the presence of pybox ligands the β-keto ester is in its enolate form. In the case of $La(OTf)_3$, **L3** and **3b** (0.4:0.4:1), no ternary specie was identified. In our last set of experiments, we performed the reaction with all the components using 25% molar of the catalyst (**L3**/$La(OTf)_3$). Samples were taken at different intervals. The ESI-MS spectra afforded the signals already observed in the ternary mixtures. Surprisingly the peak corresponding to the trifluoromethylated product **2b** could not be observed under these conditions.

The absence of species with Togni's reagent, **3b,** coordinated with lanthanide in MS-ESI studies probably indicate that very active species are formed during the reaction. The activating mode of Togni's reagent was studied by ^{19}F RMN mixing $La(OTf)_3$ and reagent **3b** (1:1) in CD_3CN. After several minutes **3b** was converted to a new species with a shift of the CF_3 from δ = -44.6 ppm to δ = -33.7 ppm. We propose the formation of the reactive cationic iodonium species **a1** (eq. 1). Other authors[31] have proposed a similar activation in the presence of other Lewis acids as $MgBr_2$[32] or CuI[12,ref] Furthermore, the appearance of a broad signal at the same δ = -33.7 ppm in the ^{19}F NMR spectrum of a mixture of all the components of the reaction, namely **1a**, **L3**, **3b** and $La(OTf)_3$ (1:0.4:1:0.4) show the coordination of **3b** to lanthanide probably given mixtures of binary and tertiary complexes.



Detailed diffusion 1H NMR experiments were carried out. The self-diffusion coefficient of **3b** was consistent with its relatively small volume (D = 2.23 10-9 m^2/s). The addition of $La(OTf)_3$ to a solution of **3b** (1:1) induced important changes showing the presence of only one species (**a1**, D = 2.00 10-9 m^2/s). Then, an experiment with a mixture of **1b**, **L3**, **3b** and $La(OTf)_3$ ((1:012:1:01) showed the formation of a unique ternary metal complex which revealed a diffusion coefficient of D = 1.48 10^{-9} m^2/s that was consistent with a large volume. Thus, the formation of a ternary complex, denoted as **INT3** in Fig. 1, was confirmed by diffusion measurements.

Next, the reaction of **1b** under the conditions described in Scheme 1 was carried out in the presence of one equivalent of two different radical scavengers (Scheme 3) such as 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) and galvinoxyl free radical [2,6-di-*tert*-butyl-α-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-*p*-tolyloxy].
After 48 hours, the reaction with TEMPO gave only trace amounts of product **2b**, but nevertheless racemic **4** was isolated in high yield (85%). The same yield was obtained directly mixing **1b** and TEMPO, suggesting that the radical reaction takes places in the absence of Togni's reagent and therefore does not provide any information about the mechanism of trifluoromethylation. However, the experiment adding galvinoxyl free radical gave exclusively the corresponding CF_3 adduct **5** (45%). The total amount of unaltered **1b** could be recovered**.** Compound **5** was first identified by a unique single signal in ^{19}F RMN at -60.1 ppm, characteristic of a O-CF_3 unit. Consequently, competition of trifluoromethyl radicals in the alkylation process cannot be discarded.



Scheme 3. Reaction of β-keto ester **1b** with radical scavengers TEMPO and Galvinoxyl.

Computational studies at the B3LYP-D3(SCRF, solvent=acetonitrile)/6-31G*&LanL2DZ level of theory[33-37] were carried out in order to get a better understanding of the experimental results. Although biradical species were searched along the catalytic cycle at the UB3LYP level, all the wave functions of the intermediate species converged to closed-shell RB3LYP solutions. From the information obtained in the ESI-MS and 2D-DOSY experiments (vide

supra), we assumed the formation, among other intermediates, of **INT1** from the reaction between La(OTf)$_3$ and chiral ligand **L3** (Figure 1). This cationic intermediate can react with ester **1b** and with an additional equivalent of **L3**, which acts as a base, to yield the enolate intermediate **INT2**, also detected by ESI-MS (vide supra), together with a **L3**·HOTf complex. This process shows a negative relative energy with respect to **INT1**, although the step is almost isoenergetic in terms of relative Gibbs energies at 298 K. Cationic intermediate **INT2** can incorporate one molecule of Togni's reagent **3b** to yield formally heptacoordinated La(III) cation **INT3**. This step is strongly exothermic and is compatible with the detection of a bulky intermediate by 2D-DOSY experiments (vide supra).

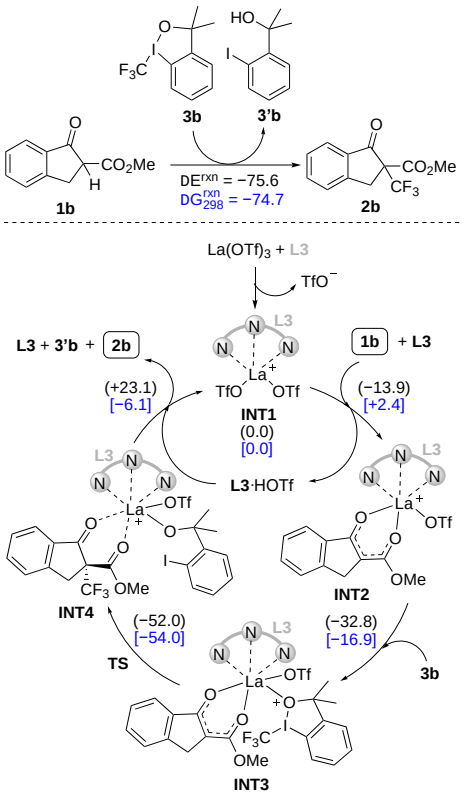


Figure 1. Proposed catalytic cycle for the formation of quaternary 2-trifluoromethyl ester ***(R)*-2b** from ***(±)*-1b** in the presence of La(OTf)$_3$, Togni's reagent **3b** and chiral ligand **L3**. Numbers in parentheses and in square brackets (in blue) correspond to the relative (with respect to **INT1**) total and Gibbs energies, respectively, in kcal/mol. These energies were calculated at the B3LYP-D3(PCM, solvent=acetonitrile)/6-31G*&LanL2DZ level of theory. The total (ΔE^{rxn}) and free (ΔG^{rxn}_{298}) reaction energies, in kcal/mol, associated with the **1b**+**3b**→**2b**+**3'b** transformation, are also given.

As far as the origin of the enantiocontrol in the formation of quaternary ester **2b** is concerned, the role of pybox ligand **L3** is readily assessed by inspection of the chief features of **INT3** (Figure 2). Thus, the coordination pattern of this cationic complex reveals an efficient blockage of the prochiral *Si* face of the La(III) enolate of **1b**. This hindrance results in an efficient S$_N$2-like saddle point **TS**, which consists of a *Re* attack of the C$_\alpha$ atom of the enolate moiety on the CF$_3$ group of **3b**, with concomitant departure of the iodine-aryl group. This linear arrangement of the C$_\alpha$···CF$_3$···I-Ar system is associated with C···C and C···I distances of ca. 2.9 Å, which corresponds to a bipyramidal geometry (see the ca. 90 deg. bond angles in the structure of **TS** gathered in Fig. 2) in which the trifluoromethyl group has a planar cationic character with a significant radical component, as revealed by its Mulliken charge of +0.58 e. This partial biradicaloid singlet character of this reaction step is compatible with the competition of radical scavengers with the trifluoromethylation process (vide supra). The activation energy associated with the C-C bond forming step was calculated to be of ca. 28 kcal/mol, a noticeable value despite the strong exergonicity of this step (Fig. 2). Once intermediate **INT4** is formed, our calculations predict the release of trifluoromethyl ester **2b**, together with 2-(2-iodoohenyl)propan-2-ol **3'b** and one equivalent of **L3** via proton transfer from the **L3**·HOTf complex (see Fig. 1). It is interesting to note that the Gibbs energy associated with this last step is the responsible for the completion of the catalytic cycle. In addition, the energy balance of the whole process is calculated to be highly exergonic (see Fig. 1) because of the energy release associated with conversion of Togni's reagent **3b** into **3'b**, which is produced during the formation of **INT4**.

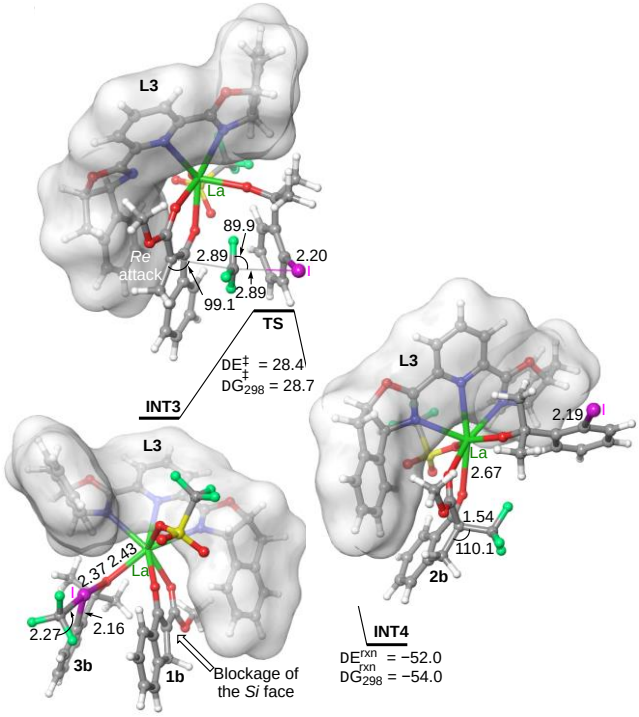


Figure 2. Fully optimized geometries of cationic intermediates **INT3** and **INT4**, connected by saddle point **TS**. Bond distances and angles are given in Å and deg., respectively. See Fig. 1 caption for additional details. The origin of the enantioselective formation of the C*···CF$_3$ bond by blockage of one of the prochiral faces of the La(III)-enolate of **1b** is highlighted.

In summary, in this communication an efficient method for the enantioselective α–trifluoromethylation of β–oxo esters is described. The reaction can proceed with high chemical yields and ee's and the origins of the enantiocontrol has been rationalized by experimental and computational methods. We think that the methods and models shown in this paper can be extended to other C-CF$_3$

bond forming reactions leading to chiral quaternary centers.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Full experimental procedures and characterization of products. Cartesian coordinates, harmonic analyses and energies of all the stationary points reported in Figs. 1 and 2 (PDF).

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REFERENCES

(1) Ismail, F. M. D. Important fluorinated drugs in experimental and clinical use. *J. Fluorine Chem.* **2002**, *118*, 27-33.
(2) Isanbor, C.; O'Hagan, D. Fluorine in medicinal Chemistry: a review of anti-cancer agents. *J. Fluorine Chem.* **2006**, *127*, 303-319.
(3) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881-1886. O'Hagan, D. Fluorine in health care: organofluorine containing blockbuster drugs. *J. Fluorine Chem.* **2010**, *131*, 1071-1081.
(4) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. Data-mining for sulfur and fluorine: an evaluation of pharmaceuticals to reveal opportunities for drug design and discovery. *J. Med. Chem.* **2014**, *57*, 2832-2842.
(5) Wang, J.; Sanchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E. Soloshonok, V. A.; Liu, H. Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001-2011). *Chem. Rev.* **2014**, *114*, 2432-2506.
(6) Smart, B. E. Fluorine substituent effect (on bioactivity). *J. Fluorine Chem.* **2001**, *109*, 3-11.
(7) Purser, S; Moore, P. R., Swallow, S. ; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320-330.
(8) Fluorine in medicinal chemistry and chemical biology, I. Ojima, Ed.; Wiley-Blackwell: Hobpken, NY **2009**.
(9) Park, B. K.; Kitteringham, N. R.; O'Neil P. M. Metabolism of fluorine-containig drugs. *Annu. Res. Pharmacol. Toxicol.* **2001**, *41*, 443-470.
(10) Ma, J.-A.; Cahard, D. Strategies for nuclephilic, electrophilic and radical trifluoromethylations. *J. Fluorine Chem.* **2007**, *128*, 975-996.
(11) Shibata, N.; Matsnev, A.; Cahard D. Shelf-stable electrophilic trifluoromethilating reagents: a brief historical perspective. *Beilstein J. Org. Chem.* **2010**, *6*, 1-19.
(12) Barata-Vallejo, S.; Lantaño, B.; Postigo, A. Recent advances in trifluoromethylation reactions with electrophilic trifluoromethylating reagents. *Chem. Eur. J.* **2014**, *20*, 16806-16829.
(13) Miró, J.; del Pozo, C. Fluorine and Gold: a fruit partnerahip. *Chem Rev.* **2016**, *116*, 11924-11966.
(14) Ma, J.-A; Cahard, D. Mild electrophilic trifluoromethylation of β-ketoesters and silyl enol ethers with 5-trifluoro methyldibenzothiophenium tetrafluoroborate. *J. Org. Chem.* **2003**, *68*, 8726-8729.
(15) Kieltsch, I.; Eisenberger, P.; Togni, A. Mild electrophilic trifluoromethylation of carbon- and sulfur- centered nucleophiles by a hypervalent iodine(III)-CF_3 reagent. *Angew. Chem. Int. Ed.* **2007**, *46*, 754-757.
(16) Noritake, S.; Shibata, N.; Nakamura, S.; Toru, T.; Shiro, M. Fluorinated Johnson reagent for transfer-trifluoromethylation to carbon nucleophiles. *Eur. J. Org. Chem.* **2008**, 3465-3468.
(17) Matsnev, A.; Noritake, S.; Nomura, Y.; Tokunaga, E.; Nakamura, S.; Shibata, N. Efficient access to extended Yagupolskii-Umemoto type reagents: triflic acid catalyzed intramolecular cyclization of *ortho*-ethynylaryltrifluoromethylsufanes. *Angew. Chem. Int. Ed.* **2010**, *49*, 572-576.
(18) Ohtsuka, Y.; Uraguchi, D.; Yamamoto, K.; Yamakawa, T. Synthesis of 2-(trifluoromethyl)-1,3-dicarbonyl compounds through direct trifluoromethylation with CF_3I and their application to fluorinated pyrazoles. *Tetrahedron* **2012**, *68*, 2636-2649.
(19) Umemoto, T.; Adachi, K. New method for trifluoromethilation of enolate anions and applications to region- diastero- and enantioselective trifluoromethylation. *J. Org. Chem.* **1994**, *59*, 5692-5699.
(20) Allen, A. E.; MacMillan D. W. C. The productive merger of iodonium salts and organocatalysis: a non-photolytic approach to the enantioselective α-trifluoromethylation of aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 4986-4987.
(21) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. Enantioselective α-Trifluoromethylation of Aldehydes via Photoredox Organocatalysis. *J. Am. Chem. Soc*. **2009**, *131*, 10875-10877.
(22) For enantioselective α-trifluorometilation of β-keto esters see: Noritake, S.; Shibata, N.; Nomura, Y.; Huang, Y.; Matnev, A.; Nakamura, S.; Toru,T.; Cahard, D. Enantiselective electrophilic trifluoromethylation of β-keto esters with Umemoto reagents induced by chiral nonracemic guanidines. *Org. Biomol. Chem.* **2009**, 7, 3599-3604.
(23) Deng, Q. -H.; Wadepohl, H.; Gade, L. H Highly enantioselective copper-catalyzed electrophilic trifluoromethylation of β-ketoesters. *J. Am. Chem. Soc.* **2012**, *134*, 10769-10772.
(24) Comelles, J.; Pericas, A.; Moreno-Mañas, M.; Vallribera, A.; Drudis-Solé, G.; Lledós, A.; Parella, T.; Roglans, A.; García-Granda, S.; Roces-Fernández, L. Highly enantioselective electrophilic amination and Michael addition of cyclic β-Keto esters induced by lanthanides and (*S,S*)-ip-pybox: the mechanism *J. Org. Chem.* **2007**, *72*, 2077-2087.
(25) Pericas, A.; Shafir, A.; Vallribera, A. Asymmetric Synthesis of L-Carbidopa based on a highly enantioselective α-amination. *Org. Lett.* **2013**, *15*, 1448-1451; Highlighted in Synfacts **2013**, *9*, 700.
(26) Pericas, A.; Jiménez, R.; Granados, A.; Shafir, A.; Vallribera, A.; Roglans, A.; Molins, E. Lanthanides-pybox: an excellent combination for highly enantioselective electrophilic α-amination of acyclic β-keto esters. Isolation of ternary pybox/Ln/β-keto ester complexes. *ChemistrySelect* **2016**, *1*, 4305-4312.
(27) Granados, A.; del Olmo, A.; Peccati, F.; Billard, T.; Sodupe, M.; Vallribera, A. Fluorous L-Carbidopa precursors: highly enantioselective synthesis and computational prediction of bioactivity. *J. Org. Chem.* **2018**, *83*, 303-313.
(28) Pericas, A.; Shafir, A.; Vallribera, A. ZnO-Catalyzed transesterification of β-keto esters. *Tetrahedron* **2008**, *64*, 9258-9263. Highlighted in *Synfacts*, **2009**, *1*, 81.
(29) Ma, B.; Lin, X.; Lin, L.; Feng, X.; Liu, X. Chiral *N,N'*-Dioxide Organocatalyzed Asymmetric Electrophilic α-Cyanation of β-Keto Esters and β-Keto Amides. *J. Org. Chem.* **2017**, *82*, 701-708.

(30) Cordi, A. A.; Lacoste, J.-M.; Descombes, J.-J.; Courchay, C.; Vanhoutte, P. M.; Laubie, M.; Verbeuren, T. J. Design, synthesis, and structure-activity relationships of a new series of .alpha.-adrenergic agonists: spiro[(1,3-diazacycylpent-1-ent)-5,2'-(1',2',3',4'-tetrahydronaphthalene)]. *J. Med. Chem.* **1995**, *38*, 4056-4069.
(31) Charpentier, J.; Fru, N.; Togni, A. Electrophilic trifluoromethylation by use of hypervalent iodine reagents. *Chem.Rev.* **2015**, *115*, 650−682.
(32) Katayev, D.; Katija, H.; Togni, A. Magnesium-catalyzed electrophilic trifluoromethylation: facile access to all-carbon quaternary centers in oxindoles. *Chem. Eur. J.* **2017**, *23*, 8353-8357.
(33) (a) Becke, A. D. Density-Functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys*. **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789.
(34) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, S. A Consistent and Accurate ab Initio Parametrization of Density Functional Dispersion Correction (DFT-D) for the 94 Elements H-Pu. *J. Chem. Phys*. **2010**, *132*, 154104−154104.
(35) (a) Cammi, R.; Mennucci, B.; Tomasi, J. First Evaluation of Geometries and Properties of Excited Molecules in Solution: A TammDoncoff Model with Application to 4-Dimethylaminobenzonitrile. *J. Phys. Chem. A.* **2000**, *104*, 5631−5637. (b) Tomasi, J.; Mennucci, B.; Cammi, R. Quantum Mechanical Continuum Solvatation Models. *Chem. Rev.* **2005**, *105*, 2999−3094.
(36) Wadt, W. R.; Hay, P. J. *Ab initio* effective core potentials for molecular calculations. Potentials for K to Au including the outermost core orbitals *J. Chem. Phys.* **1985**, *82*, 284-299.
(37) Frisch, M. J., et al. Gaussian 09, revision D.01; Gaussian, Inc.: Wallingford, CT, **2009** (full reference in the Supporting Information).