Advanced Synthesis & Catalysis

Accepted Article

Title: Ruppert-Prakash Reagent (TMSCF3)-Catalyzed Chemoselective Esterification of Weinreb Amides

Authors: Margherita Miele, Laura Castoldi, Egle Beccalli, and Vittorio Pace

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.202400008

Link to VoR: https://doi.org/10.1002/adsc.202400008

10.1002/adsc.202400008

RESEARCH ARTICLE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Ruppert-Prakash Reagent ($TMSCF_3$)-Catalyzed Chemoselective Esterification of Weinreb Amides

Margherita Miele,[a,b] Laura Castoldi,[c] Egle Beccalli[c] and Vittorio Pace[a,b*]

[a] University of Vienna, Department of Pharmaceutical Sciences, Division of Pharmaceutical Chemistry - Josef-Holaubek-Platz 2, 1090, Vienna, Austria. e-mail: vittorio.pace@univie.ac.at
[b] University of Turin, Department of Chemistry, Via P. Giuria 7 – 10125 Turin (Italy) – e-mail; vittorio.pace@unito.it. Tel. +39-011-6707934
[c] University of Milan - Department of Pharmaceutical Sciences, General and Organic Chemisty Section "A. Marchesini" – Via Venezian 21, 20133 Milan, Italy.

Dedicated to Professor Guido Viscardi in the occasion of his retirement

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A straightforward $TMSCF_3$-catalyzed conversion of Weinreb amides into esters through the treatment with sodium alkoxides is reported. The procedure documents a genuine selectivity for the esterification of primary alcohols with Weinreb amides featuring diverse substitution pattern. The constitutive *N*-methoxy fragment of these acylating agents is responsible for the unique reactivity they display, thus enabling to explore alkoxides as competent nucleophilic elements. The protocol is compatible with the fully transfer of stereochemical information embodied in the starting material, as well as, guarantees the preparation of pharmaceuticals. Mechanistic investigations revealed that under the adopted reaction conditions (NaOR, R primary) $TMSCF_3$ does not release the trifluoromethyl (CF_3^-) anion – as occurs with tertiary alkoxides - but rather it catalytically activates the amidic bond.

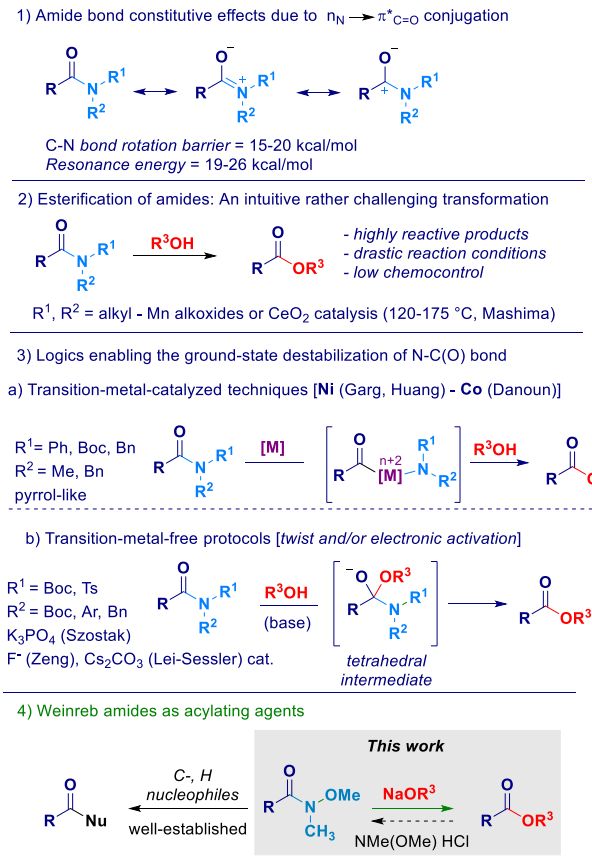
Keywords: Amides; Esterification; Chemoselectivity; Nucleophilic substitution; Alkoxides.

Introduction

The amide linkage constitutes the most ubiquitous chemical functionality expressed in Nature.[1] As a consequence of the delocalization between the nitrogen lone pair and the carbonyl motif ($n_N \rightarrow \pi^*_{C=O}$ conjugation), amides exhibit high thermodynamic stability (Scheme 1 – *path 1*).[2] This constitutive characteristic – making amides almost inert substrates according to a classical paradigm in Chemistry[3] - is responsible for their widespread utilization as a robust functionality.[4] Notwithstanding, the chemical modification of amides in biological systems occurs under mild conditions in the presence of (metallo)-enzymes.[5] As a general rule, formal nucleophilic addition/elimination sequences on amides deliver intrinsically more reactive products (*e.g.* ketones) which may affect the chemoselectivity of processes.[6] In such a context, the esterification of amides represents an attractive transformation due to the reach portfolio of operations attainable with this class of products.[7] Before the advent of valuable technologies enabling the challenging nucleophilic attack to the amide carbonyl *via* electrophilic activation,[8] the adoption of drastic conditions was critical to ensure reactivity.[9] Elegant work by Mashima showed the effectiveness of dinuclear Mn alkoxides complexes for catalytically esterifying *N*,*N*-dialkylamides at high temperatures (120-175 °C),[10] while by using CeO_2 also primary amides could undergo similar processes (*path 2*).[11] In order to engage amides as competent electrophilic synthons under less stressful regime, it is essential overcoming the thermodynamic barrier imparted by the N-C(O) delocalization.[12] Firstly explored rationales involved the complexation of the nitrogen or the carbonyl lone pairs with (stoichiometric) loading of metals.[13] Moreover, the structural deformation of the amide bond - *i.e. via* deviation from planarity by introducing twisted - emerged as an attractive logic for the interconversion of these building blocks under relatively mild transition-metal catalytic conditions.[14] Despite these significant advancements, enrolling more stable tertiary

10.1002/adsc.202400008

amides as competent partners in esterifications proved to be a huge challenge. A breakthrough was introduced by Garg in 2015 who showed the oxidative addition of a Ni(0)-NHC-catalyst for forming an acyl-metal intermediate amenable for reacting with a nucleophilic alcohol (*path 3a*).[15] Conceptually analogous ground-state destabilization of the N-C(O) bond has been achieved through the use of cobalt-catalysis.[16] However, the productivity of the oxidative addition is dependent on the substitution level of the amide, thus making desirable establishing more general methods. Although - in principle - deemed highly difficult, the adoption of transition-metal-free logics levered on the assembly of tetrahedral intermediates, resulted an excellent tool for esterifying substituted amides. Zeng documented the use of a fluoride-catalyst acting as a strong nucleophilic element for attacking the amide carbonyl prior to the addition of the alcohol.[17] Szostak demonstrated that the transition-metal-free esterification of amides could be performed under highly convenient mild conditions from rationally designed twisted amides (*path 3b*).[18] Furthermore, the employment of caesium carbonate as a catalyst enabled to extend the strategy to aliphatic alcohols, as documented by Sessler and Lei.[19] In recent years, the N-C(O) linkage breaking[20] of amides *en route* to esters benefited from additional implementations such as the hydrogen-bond assisted transition-metal-free catalysis,[21] the Pd-catalyzed aerobic oxidative or, the transition-free DMAP-mediated coupling with boronic acids.[22]



Scheme 1. Esterification of amides: state-of-the-art.

We reasoned that the reaction of an alkoxide with Weinreb amides,[23] a class of standard acylating agents,[24] would represent an attractive synthetic tool for preparing esters through a conceptually intuitive protocol (*path 4*). Remarkably, since the introduction in 1981, their use as acylating platforms has been almost restricted to carbon-centered[25] and hydride[26] nucleophiles to access carbonyl and alkene motifs. Except for the hydrolysis (yielding carboxylic acids),[27] to the best of our knowledge, acylation operations with heteroatom-based nucleophilic elements remain unexplored. Of note, the inverse process (*i.e.* conversion of esters to Weinreb amides) is one of the best methods for preparing *N*-methyl-*N*-methoxyamides.[23] Herein, we document the chemoselective transformation of Weinreb amides into esters *via* the reaction of primary alkoxides in the presence of $TMSCF_3$ as a competent Lewis acid catalyst.

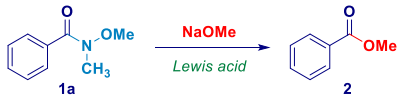
Results and Discussion

The reaction between Weinreb amide **1a** and a commercially available solution of NaOMe in MeOH was selected as the model case (Table 1). After 72 h in THF, the starting material was completely transformed into ester **2**, thus showing the feasibility of the process (entry 1). Changing solvent or increasing temperature had little effect on shortening the reaction time (entries 2-4). The

10.1002/adsc.202400008

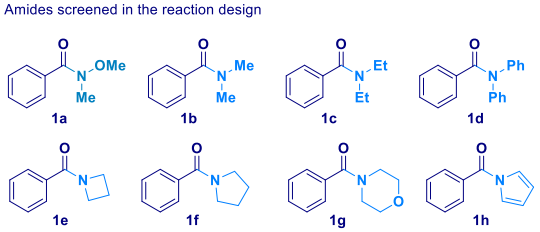
addition of Lewis acids such as $Sc(OTf)_3$ or $B(C_6F_5)_3$ for enhancing the amide carbonyl electrophilicity – had a detrimental effect (entries 5-6). However, the switching to the silicon-centered analogue $SiCl_4$ was effective (entry 7) and enabled to obtain **2** in considerably shorter times (overnight, 12 h), also when employed at catalytic loading (entry 8). While the weaker Lewis acid TMSCl was ineffective (entry 9), an excellent performance was observed with $TMSCF_3$ (Ruppert-Prakash reagent)[28] which furnished ester **2** in nearly quantitative yield (entry 10). Conducting the esterification on a Weinreb amide was essential (*vide infra*): different analogues including tertiary amides (**1b-1d**), acyl-azetidine (**1e**),[29] acyl-pyrrolidine (**1f**),[30] acyl-morpholine (**1g**)[31] – known to be acylating agents with *C*-nucleophiles - were not suited for promoting the reaction (entry 11). Although at a significant less extent, the only substrate amenable for the transformation was *N*-acypyrrole (**1h**) presumably as a consequence of the higher electrophilicity of the amide carbonyl resulting from diminished delocalization of its nitrogen lone pair (entry 12).[32] Finally, it was possible to use different alkali metal alkoxides, being LiOMe comparable in terms of yield to NaOMe (entries 13-14).

Table 1. Reaction optimization.



Entry	Amide	Lewis acid (equiv)	Solvent	Reaction time (h)	Yield of **2** (%)[a]
1	**1a**	-	THF	72	78
2[b]	**1a**	-	THF	72	81
3	**1a**	-	MeCN	72	53
4	**1a**	-	MeOH	72	64
5	**1a**	$Sc(OTf)_3$ (1.0)	THF	72	26
6	**1a**	$B(C_6F_5)_3$ (1.0)	THF	72	38
7	**1a**	$SiCl_4$ (1.0)	THF	12	84
8	**1a**	$SiCl_4$ (0.2)	THF	12	82
9	**1a**	TMSCl (0.2)	THF	12	traces
10	**1a**	$TMSCF_3$ (0.2)	THF	12	95
11	**1b-1g**	$TMSCF_3$ (0.2)	THF	12	-
12	**1h**	$TMSCF_3$ (0.2)	THF	12	61
13[c]	**1a**	$TMSCF_3$ (0.2)	THF	12	76
14[d]	**1a**	$TMSCF_3$ (0.2)	THF	12	92

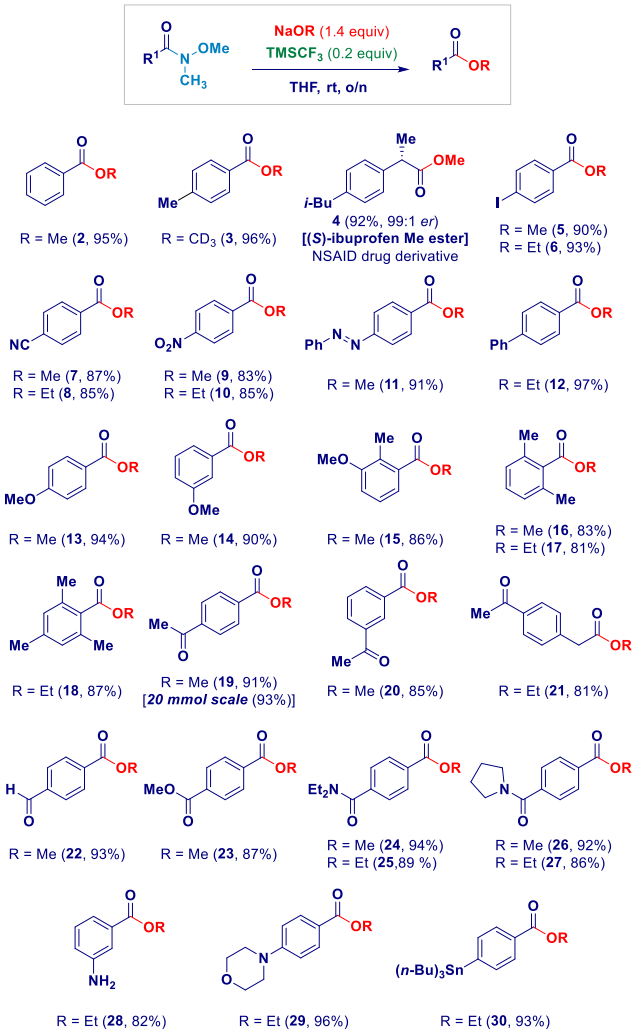
Amides screened in the reaction design



[a] Otherwise stated reactions were with NaOMe 25% wt solution in MeOH at room temperature. Yields refer to the isolated product after eventual purification. [b] Reaction performed at 50 °C. [c] KOMe 25% wt solution in MeOH was used. [d] LiOMe 1 M solution in MeOH was used.

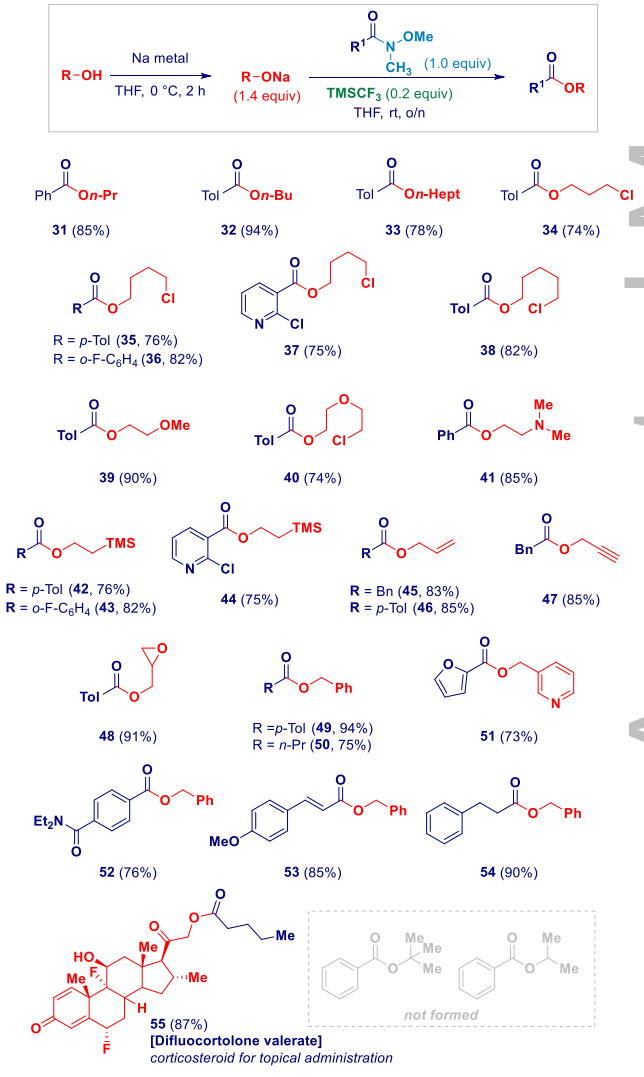
Having established the optimal conditions for forming esters from Weinreb amides, the scope of the method was then studied with either NaOMe and NaOEt (Scheme 2), being also adaptable for preparing the labeled CD_3 analogue **3**. We were delighted in fully maintaining (**4**) the optical information of the enantiomerically pure Weinreb amide - derived from the common NSAID drug Ibuprofene - potentially susceptible of sequential enolate formation / racemization at the benzylic position. Wide flexibility on the nature of substituents positioned on the starting materials was allowed. Thus, methyl and ethyl esters presenting halogen- (**5-6**), cyano- (**7-8**), nitro- (**9-10**), phenylazo- (**11**) and aryl- (**12**) substituents were prepared in efficient yields without affecting the chemical integrity of these functionalities. Electron-donating substituents (**13-15**) taming the amides electrophilicities were not detrimental for the protocol. Notably, the presence of sterically demanding elements [2,6-dimethylphenyl (**16-17** and mesityl (**18**)] did not alter the effectiveness, thus allowing the rapid preparation of congested esters. The selectivity of the protocol towards carbonyl-containing Weinreb amides was superb. As documented by models including ketones (**19-21**), alkoxides performed selective attacks to the *N*-methyl-*N*-methoxyamide site. Some additional points merit mention: a) despite the acidity of acetophenone- (**19-20**) and homobenzoate-derivatives, no enolization was evidenced; b) scaling up the methodology to 20 mmol loading retained the efficiency (93% isolated yield); c) running the reaction on a formyl derivative was equally successful, giving the aldehyde-containing ester **22**; d) a mixed ester-Weinreb amide yielded the corresponding diester product **23** under the optimized reaction conditions, thus highlighting the compatibility with esters, as well. As expected from the optimization study, Weinreb acylating agents featuring diverse amide functionalities [*N*,*N*-diethyl- (**24-25**) and *N*-pyrrolidinyl (**26**)] were exclusively esterified at the *N*-methyl-*N*-methoxyamide fragment, with no modification on these pre-installed functional groups. Moreover, amine moieties [primary (**28**) and tertiary (*N*-morpholinyl, **29**)] were similarly tolerated. We were pleased to validate the methodology also for a Weinreb amide presenting a C-metal bond, as indicated by the versatile stannyl analogue **30**.

10.1002/adsc.202400008



Scheme 2. Scope of the reaction: synthesis of methyl and ethyl esters from Weinreb amides.

The smooth preparation of sodium alkoxides according to known protocols,[33] allowed to further extend the application of the Weinreb amide esterification by strategically selecting the corresponding hydroxy precursor (Scheme 3). Aliphatic alcohol of variable length chain furnished esters with high efficiency (**31**-**33**). With the aim to access esters amenable for subsequent nucleophilic displacements, a series of homologous aliphatic alcohols presenting ω-chloro substituents were used for preparing under remarkable chemocontrol the corresponding alkoxides and, then coupled with the Weinreb amides. Although potentially susceptible of chlorine-metal exchange phenomena, the expected esters (**34**-**38**) were formed in high yield. Analogously, glycol-type containing nucleophilic elements underwent the acylation without difficulties (**39**-**40**), as well as, a β-*N*,*N*-dimethylaminoethyl alcohol (**41**). Embodying a metal-carbon bond in the alkoxide precursor was again possible, as noticed for silyl analogues **42**-**44**. Allyloxy sodium was a competent reaction partner for both alkyl- (**45**) and aryl- Weinreb amide (**46**); moreover, also propargylic alcohol furnished the ester in high yield (**47**). Diversifying the chemical nature of the primary alkoxide further expanded the scope, as noticed in the cases of epoxy-alcohol (glycidol, **48**) and (hetero)benzyl-type systems (**49**-**51**). The chemocontrol of the method was further observed in the preparation of derivative **52** exhibiting a *N*,*N*-diethyl-amide functionality inert under the esterifying conditions. Cinnamoyl- (**53**) and its saturated analogue (dihydrocynnamoil, **54**) further strengthened the significance of the technique. The broad utility of the transformation is additionally validated by the smooth preparation of the steroid pharmaceutical difluocortolone valerate **55**: despite the presence of a secondary alcohol – among other potentially susceptible motifs (*e.g.* ketones, alkenes) - only the primary one was esterified. In this sense, the genuine chemoselective profile for primary alcohols was confirmed by the lack of reactivity of NaO*t*Bu and NaO*i*Pr.



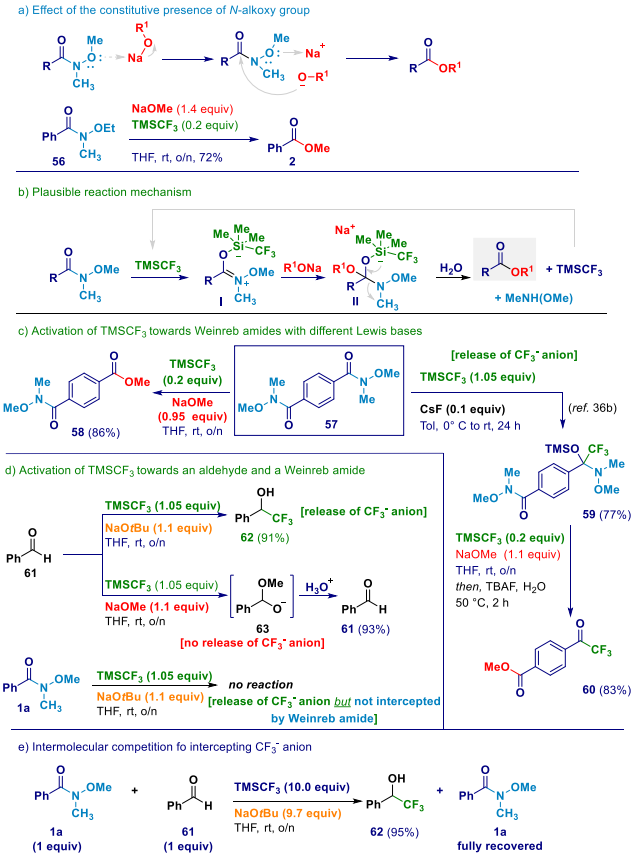
10.1002/adsc.202400008

Scheme 3. Synthesis of diverse esters from Weinreb amides and prepared alkoxides.

The mechanistic investigation revealed a dual dependance from: a) the Weinreb amide functionality and, b) the effect of $TMSCF_3$ (Scheme 4). The constitutive *N*-methoxy group could coordinate the cation thus, enabling the attack of the alkoxide to the carbonyl (*path a*). This element is consistent with the experimental result that even in the absence of $TMSCF_3$, the reaction is productive, though longer times are required (Table 1). It also explains the unique reactivity of Weinreb amides compared to other screened systems lacking the coordinating *N*-methoxy element (see above, Table 1). As an additional proof, the use of the modified Weinreb amide [*N*-ethoxy-*N*-methyl- congener (**56**)][34] furnished the desired product (**2**), thus confirming the requirement for a *N*-alkoxy functionality in the starting amide. The role of $TMSCF_3$ is more intriguing. It is well known that it represents a *reservoir* of the labile CF_3 anion[28b] delivered upon the collapse of a pentacoordinate silicon-ate complex resulting from the attack of a Lewis base to the electrophilic silicon.[35] Indeed, in the present case, the carbonyl oxygen of the Weinreb amide could attack – spurred by mesomerism – the silicon, giving complex **I** (*path b*). Therefore, the alkoxide would perform the nucleophilic addition/elimination sequence (**II**), finally yielding the ester and regenerating $TMSCF_3$ able to commence the esterification of a new Weinreb amide molecule. This would explain the afore-mentioned unproductivity of secondary and tertiary alkoxides whose bulkiness would hamper the efficient attack for forming the tetrahedral intermediate **II**.

With the aim to decipher the role of $TMSCF_3$, an investigation of its reactivity in the presence of different Lewis bases activators was performed. We would exclude the genesis of the trifluoromethyl anion (CF_3^-) under our reaction conditions. In this sense, Leadbeater[36] and Grellepois-Portella[37] reported the preparation of CF_3-ketones from Weinreb amides and initiators such as CsF, TBAF or TBAT, thus highlighting the critical role of the Lewis base in determining the reaction outcome.[38] By reacting bis-Weinreb amide **57** with NaOMe (0.95 equiv), esterification took place at only one of the two possible positions, yielding *p*-methoxycarbonyl Weinreb benzamide **58** (*path c*). Moreover, also by increasing the loading of $TMSCF_3$, no trifluoromethylketone was obtained.[36c, 39] These experiments were consistent with no formation of the CF_3^- anion, thus suggesting that a primary alkoxide is not suited for activating $TMSCF_3$ towards the carbanion release. Conversely, when the same amide **57** is treated under Leadbeater's conditions (CsF),[36b] adduct **59** featuring a hemiaminal moiety[40] resulting from the attack of the CF_3^- anion to the Weinreb amide was generated. The subsequent addition of $TMSCF_3$ (0.2 equiv) to **59** – *but followed by the treatment with NaOMe* – furnished *p*-(trifluoroacetyl) benzoic acid methyl ester **60**, thus confirming the hypothesis that the system $TMSCF_3$/NaOMe does not generate CF_3^-. In order to generalize these conclusions, we therefore run $TMSCF_3$-mediated operations on (the more electrophilic) benzaldehyde **61** (*path d*). When NaO*t*Bu was employed – as the initiator - trifluoromethylated alcohol **62** was easily formed, whereas by using NaOMe the aldehyde motif was recovered, presumably due to the formation of a unstable hemiacetal **63** which collapsed restoring the carbonyl group (**61**). Collectively, these experiments confirm two key features: *i*) a tertiary alkoxide (NaO*t*Bu) efficiently activates $TMSCF_3$ towards the release of CF_3^- which – being a weak nucleophile - can attack only strong electrophiles (aldehydes) whereas, *ii*) a primary alkoxide (NaOMe) is at all not a competent activator for $TMSCF_3$. Additional evidence arises from an intermolecular experiment (*path e*) consisting in treating a 1:1 mixture of Weinreb amide **1a** and benzaldehyde **61** with an excess of $TMSCF_3$ and NaO*t*Bu. Exclusively trifluoromethyl-alcohol **62** was formed, while the Weinreb amide **1a** – a weaker electrophile - was fully recovered.

10.1002/adsc.202400008



Scheme 4. Mechanistic investigations and role of $TMSCF_3$.

Conclusion

In summary, we have disclosed a conceptually intuitive conversion of Weinreb amides into esters *via* the straightforward treatment with alkoxides in the presence of the Ruppert-Prakash reagent acting as a versatile catalyst. The protocol documents a wide substrate scope, being flexible for productively engaging as competent partners variously substituted Weinreb amides and sodium alkoxides. Of note, the complete transfer of the stereochemical information embodied in the starting amide and, the genuine chemocontrol observed with materials featuring potentially sensitive functional groups, including the steroid agent difluocortolone valerate. The methodology is paved on the unique constitutive effect of the *N*-alkoxy moiety of the Weinreb amide acting as a coordinating element for the alkoxides, thus formally enhancing their nucleophilicity. The catalytic role of $TMSCF_3$ is presumably ascribed to the formation of an *ate* complex with the amide carbonyl, thus formally boosting its electrophilicity. Mechanistic investigations are consistent with the exclusion of the formation of the trifluoromethyl anion under the reaction conditions. Finally, this work introduces new acylating sequences for well-known and easy to prepare Weinreb amides, thus extending the portfolio of these valuable acylating agents also to non-carbon centered or hydride nucleophiles.

Experimental Section

General procedure for the esterification of Weinreb amides with a primary sodium alkoxide.

To a solution of Weinreb amide (1.0 equiv) in dry THF (3 mL) cooled at 0 °C, trimethyl(trifluoromethyl)silane was added (0.2 equiv) under Argon atmosphere. After 5 min, the solution of the competent alkoxide (1.4 equiv) was added dropwise during a period of 15 min and, the stirring was continued overnight at room temperature. Subsequently, the mixture was quenched with saturated (*aq.*) NH_4Cl (3 mL) and extracted with dichloromethane (3 mL). The organic layer was washed with saturated (*aq.*) NaCl (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude compound purified as indicated below.

.

Acknowledgements

The Authors are indebted to the Universities of Turin, Vienna and Milan for financial support. All-4-Labels (Hamburg, Germany) is gratefully acknowledged for funding this research. Project CH4.0 under MUR (Italian Ministry for the University) program “Dipartimenti di Eccellenza 2023-2027” (CUP: D13C22003520001) is acknowledged.

References

[1] For comprehensive discussions, see: a) A. Greenberg, C. M. Breneman, J. F. Liebman, *The Amide Linkage. Selected Structural Aspects in Chemistry, Biochemistry and Materials Science*, John Wiley & Sons Inc., New York, **2000**; b) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471-479.
[2] For an exhaustive overview of key aspects of the amide bond, see: a) G. Li, S. Ma, M. Szostak, *Trends Chem.* **2020**, *2*, 914-928; b) L. Pauling, *The Nature of the Chemical Bond*, Oxford University Press, London, **1940**; c) K. B. Wiberg, *Acc. Chem. Res.* **1999**, *32*, 922-929.
[3] For a critical discussion, see: D. Kaiser, N. Maulide, *J. Org. Chem.* **2016**, *81*, 4421-4428.
[4] a) M. Gehringer, S. A. Laufer, *J. Med. Chem.* **2019**, *62*, 5673-5724; b) L. Crespo, G. Sanclimens, M. Pons, E. Giralt, M. Royo, F. Albericio, *Chem. Rev.* **2005**, *105*, 1663-1682.
[5] a) B. W. Matthews, *Acc. Chem. Res.* **1988**, *21*, 333-340; For a recent example of biomimetic approach of amides esterification, see: b) C. C. D. Wybon, C. Mensch, C. Hollanders, C. Gadais, W. A. Herrebout, S. Ballet, B. U. W. Maes, *ACS Catal.* **2018**, *8*, 203-218.
[6] For reviews, see: a) L. Guo, M. Rueping, *Acc. Chem. Res.* **2018**, *51*, 1185-1195; b) N. A. Afagh, A. K. Yudin, *Angew. Chem. Int. Ed.* **2010**, *49*, 262-310.

[7] a) J. Otera, J. Nishikido, *Esterification: Methods, Reactions, and Applications*, 2nd ed., Wiley-VCH, Weinheim, **2010**.
[8] For comprehensive reviews on the reactivity of amides *via* nucleophilic addition/elimination sequences, see: a) V. Pace, W. Holzer, B. Olofsson, *Adv. Synth. Catal.* **2014**, *356*, 3697-3736; b) D. Kaiser, A. Bauer, M. Lemmerer, N. Maulide, *Chem. Soc. Rev.* **2018**, *47*, 7899-7925; c) H. Pei-Qiang, *Acta Chim. Sinica* **2018**, *76*, 357-365; d) V. Pace, W. Holzer, *Aust. J. Chem.* **2013**, *66*, 507-510; e) M. Blangetti, K. de la Vega-Hernández, M. Miele, V. Pace, in *Amide Bond Activation* (Ed.: M. Szostak), Wiley-VCH, Weinheim, 2022, pp. 101-156; For seminal works on amide activation with electrophilic reagents, see: f) W. S. Bechara, G. Pelletier, A. B. Charette, *Nat. Chem.* **2012**, *4*, 228-234; g) K.-J. Xiao, A.-E. Wang, P.-Q. Huang, *Angew. Chem. Int. Ed.* **2012**, *51*, 8314-8317; For a remarkable example of amide esterification promoted by Tf_2O, see: h) A. B. Charette, P. Chua, *Synlett* **1998**, 163-165.
[9] For a comprehensive review on amides esterification, see: K. Mashima, T. Hirai, H. Nagae, in *Amide Bond Activation* (Ed.: M. Szostak), Wiley-VCH, Weinheim, 2022, pp. 221-241.
[10] a) H. Nagae, T. Hirai, D. Kato, S. Soma, S.-y. Akebi, K. Mashima, *Chem. Sci.* **2019**, *10*, 2860-2868. b) T. Hirai, D. Kato, B. K. Mai, S. Katayama, S. Akiyama, H. Nagae, F. Himo, K. Mashima, *Chem. Eur. J.* **2020**, *26*, 10735-10742; For a detailed account, see c) K. Mashima, Y. Nishii, H. Nagae, *Chem. Rec.* **2020**, *20*, 332-343.
[11] a) S. M. A. H. Siddiki, A. S. Touchy, M. Tamura, K.-i. Shimizu, *RSC Adv.* **2014**, *4*, 35803-35807; b) T. Toyao, M. Nurnobi Rashed, Y. Morita, T. Kamachi, S. M. A. Hakim Siddiki, M. A. Ali, A. S. Touchy, K. Kon, Z. Maeno, K. Yoshizawa, K.-i. Shimizu, *ChemCatChem* **2019**, *11*, 449-456.
[12] C. R. Kemnitz, M. J. Loewen, *J. Am. Chem. Soc.* **2007**, *129*, 2521-2528.
[13] a) M. C. Bröhmer, S. Mundinger, S. Bräse, W. Bannwarth, *Angew. Chem. Int. Ed.* **2011**, *50*, 6175-6177; b) U. Jakob, S. Mundinger, W. Bannwarth, *Eur. J. Org. Chem.* **2014**, *2014*, 6963-6974.
[14] For excellent reviews, see: a) M. Szostak, J. Aubé, *Chem. Rev.* **2013**, *113*, 5701-5765; b) C. Liu, M. Szostak, *Chem. Eur. J.* **2017**, *23*, 7157-7173; c) G. Meng, J. Zhang, M. Szostak, *Chem. Rev.* **2021**, *121*, 12746-12783. For remarkable examples of sterically hindered amides esterification, see: d) M. Hutchby, C. E. Houlden, M. F. Haddow, S. N. G. Tyler, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2012**, *51*, 548-551; e) S. Yamada, *Angew. Chem. Int. Ed.* **1993**, *32*, 1083-1085; f) W. E. Doering, J. D. Chanley, *J. Am. Chem. Soc.* **1946**, *68*, 586-588; g) A. J. Kirby, I. V. Komarov, P. D. Wothers, N. Feeder, *Angew. Chem. Int. Ed.* **1998**, *37*, 785-786.
[15] For seminal work, see: a) L. Hie, N. F. Fine Nathel, T. K. Shah, E. L. Baker, X. Hong, Y.-F. Yang, P. Liu, K. N. Houk, N. K. Garg, *Nature* **2015**, *524*, 79-83; b) L. Hie, E. L. Baker, S. M. Anthony, J.-N. Desrosiers, C. Senanayake, N. K. Garg, *Angew. Chem. Int. Ed.* **2016**, *55*, 15129-15132; c) B. J. Simmons, N. A. Weires, J. E. Dander, N. K. Garg, *ACS Catal.* **2016**, *6*, 3176-3179; d) T. B. Boit, A. S. Bulger, J. E. Dander, N. K. Garg, *ACS Catal.* **2020**, *10*, 12109-12126; e) T. Deguchi, H.-L. Xin, H. Morimoto, T. Ohshima, *ACS Catal.* **2017**, *7*, 3157-3161; f) H. Chen, D.-H. Chen, P.-Q. Huang, *Sci. China Chem.* **2020**, *63*, 370-376; For detailed perspectives, see: g) J. E. Dander, N. K. Garg, *ACS Catal.* **2017**, *7*, 1413-1423; h) L. Hie, T. K. Shah, in *Amide Bond Activation* (Ed.: M. Szostak), Wiley-VCH, Weinheim, 2022, pp. 243-272.
[16] a) Y. Bourne-Branchu, C. Gosmini, G. Danoun, *Chem. Eur. J.* **2017**, *23*, 10043-10047; For detailed reviews on the activation of amides with transition metals, see: b) M. B. Chaudhari, B. Gnanaprakasam, *Chem. Asian J.* **2019**, *14*, 76-93; c) S. Shi, S. P. Nolan, M. Szostak, *Acc. Chem. Res.* **2018**, *51*, 2589-2599; d) R. Takise, K. Muto, J. Yamaguchi, *Chem. Soc. Rev.* **2017**, *46*, 5864-5888.
[17] a) H. Wu, W. Guo, S. Daniel, Y. Li, C. Liu, Z. Zeng, *Chem. Eur. J.* **2018**, *24*, 3444-3447; For additional uses of CsF in amides transformations, see: b) W. Guo, J. Huang, H. Wu, T. Liu, Z. Luo, J. Jian, Z. Zeng, *Org. Chem. Front.* **2018**, *5*, 2950-2954; c) Z. Luo, H. Wu, Y. Li, Y. Chen, J. Nie, S. Lu, Y. Zhu, Z. Zeng, *Adv. Synth. Catal.* **2019**, *361*, 4117-4125. Three examples of esters obtained from tertiary amides *via* radical-polar crossover have been reported. The protocol is levered on the initial formation of an acyl fluoride from the amide. See: d) Z. Wang, A. Matsumoto, K. Maruoka, *Chem. Sci.* **2020**, *11*, 12323-12328.
[18] G. Li, P. Lei, M. Szostak, *Org. Lett.* **2018**, *20*, 5622-5625.
[19] D. Ye, Z. Liu, H. Chen, J. L. Sessler, C. Lei, *Org. Lett.* **2019**, *21*, 6888-6892.
[20] K. Ouyang, W. Hao, W.-X. Zhang, Z. Xi, *Chem. Rev.* **2015**, *115*, 12045-12090.
[21] C. Huang, J. Li, J. Wang, Q. Zheng, Z. Li, T. Tu, *Sci. China Chem.* **2021**, *64*, 66-71.
[22] a) T. Wang, Y. Wang, K. Xu, Y. Zhang, J. Guo, L. Liu, *Eur. J. Org. Chem.* **2021**, *2021*, 3274-3277; b) H. Ding, W.-Y. Qi, J.-S. Zhen, Q. Ding, Y. Luo, *Tetrahedron Lett.* **2020**, *61*, 152444.
[23] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815-3818.
[24] For a recent reviews, see: a) J. Kalepu, L. T. Pilarski, *Molecules* **2019**, *24*, 830-852.; b) S. Balasubramaniam, I. S. Aidhen, *Synthesis* **2008**, 3707-3738.
[25] For reviews on the addition of carbon-centered nucleophiles, see: a) R. Senatore, L. Ielo, S. Monticelli, L. Castoldi, V. Pace, *Synthesis* **2019**, *51*, 2792-2808; b) T. Sato, N. Chida, *Org. Biomol. Chem.* **2014**, *12*, 3147-3150; c) T Sato, M. Yoritate, H. Tajima, N. Chida, *Org. Biomol. Chem.* **2018**, *16*, 3864-3875; For a recent example from our group, see: d) V. Pace, L. Castoldi, W. Holzer, *J. Org. Chem.* **2013**, *78*, 7764-7770; For the addition of phosphorous ylides to Weinreb amides, see: e) J. A. Murphy, A. G. J. Commeureuc, T. N. Snaddon, T. M. McGuire, T. A. Khan, K. Hisler, M. L. Dewis, R. Carling, *Org. Lett.* **2005**, *7*, 1427-1429; f) K. Hisler, R. Tripoli, J. A. Murphy, *Tetrahedron Lett.* **2006**, *47*, 6293-6295; For remarkable examples of nucleophilic addtions to *N*-alkoxyamides, see: g) Y. Yanagita, H. Nakamura, K. Shirokane, Y. Kurosaki, T. Sato, N. Chida, *Chem. Eur. J.* **2013**, *19*, 678-684; h) K. Shirokane, Y. Kurosaki, T. Sato, N. Chida, *Angew. Chem. Int. Ed.* **2010**, *49*, 6369-6372; i) G. Vincent, R. Guillot, C. Kouklovsky, *Angew. Chem. Int. Ed.* **2011**, *50*, 1350-1353; j) M. Nakajima, Y. Oda, T. Wada, R. Minamikawa, K. Shirokane, T. Sato, N. Chida, *Chem. Eur. J.* **2014**, *20*, 17565-17571. See also refs. 8a-e.
[26] a) J. T. Spletstoser, J. M. White, A. R. Tunoori, G. I. Georg, *J. Am. Chem. Soc.* **2007**, *129*, 3408-3419; b) J. M. White, A. R. Tunoori, G. I. Georg, *J. Am. Chem. Soc.* **2000**, *122*, 11995-11996; c) C. L. Bailey, J. W. Clary, C. Tansakul L. Klabunde, C. L. Anderson, A. Y. Joh, A. T. Lill, N. Peer, R. Braslau, B. Singaram, *Tetrahedron Lett.* **2015**, *56*, 706-709.
[27] a) K. E. Rodriques, *Tetrahedron Lett.* **1991**, *32*, 1275-1278.
[28] For excellent reviews, see: a) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757-786; b) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683-730. For a recent study highlighting multifunctional roles of $TMSCF_3$, see (c) Cai, Y.; Zhu, W.; Zhao, S.; Dong, C.; Xu, Z.; Zhao, Y. *Org. Lett.* **2021**, *23*, 3546-3551.
[29] C. Liu, M. Achtenhagen, M. Szostak, *Org. Lett.* **2016**, *18*, 2375-2378.

[30] S. Ghinato, D. Territo, A. Maranzana, V. Capriati, M. Blangetti, C. Prandi, *Chem. Eur. J.* **2021**, *27*, 2868-2874.
[31] S. Sengupta, S. Mondal, D. Das, *Tetrahedron Lett.* **1999**, *40*, 4107-4110.
[32] D. A. Evans, G. Borg, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2002**, *41*, 3188-3191. See also ref. 40.
[33] K. Das, P. G. Nandi, K. Islam, H. K. Srivastava, A. Kumar, *Eur. J. Org. Chem.* **2019**, 6855-6866. Although also NaOPh could be easily generated, the corresponding *O*-phenyl ester was not formed. Similarly, the protocol did not afford an amide upon treating a deprotonated aniline (*p*-bromoaniline / LHDMS) with a Weinreb amide.
[34] M. Malik, R. Senatore, T. Langer, W. Holzer, V. Pace, *Chem. Sci.* **2023**, *14*, 10140-10146.
[35] H. J. Reich, in *Lewis Base Catalysis in Organic Synthesis* (Eds.: E. Vedejs, S. E. Denmark), Wiley-VCH, Weinheim, 2016, pp. 233-280.
[36] a) C. B. Kelly, M. A. Mercadante, N. E. Leadbeater, *Chem. Commun.* **2013**, *49*, 11133-11148; b) D. M. Rudzinski, C. B. Kelly, N. E. Leadbeater, *Chem. Commun.* **2012**, *48*, 9610-9612. When compound **57** was reacted with an excess of $TMSCF_3$ (10 equiv) and NaOMe (0.95 equiv), the only product was **58** (91% yield).
[37] a) A. Ben Jamaa, M. Latrache, E. Riguet, F. Grellepois, *J. Org. Chem.* **2020**, *85*, 9585-9598; b) J. Nonnenmacher, F. Massicot, F. Grellepois, C. Portella, *J. Org. Chem.* **2008**, *73*, 7990-7995.
[38] For an extensive study on the Lewis base activation of the Ruppert-Prakash reagent, see: G. K. S. Prakash, C. Panja, H. Vaghoo, V. Surampudi, R. Kultyshev, M. Mandal, G. Rasul, T. Mathew, G. A. Olah, *J. Org. Chem.* **2006**, *71*, 6806-6813.
[39] a) Y. Zhao, W. Huang, J. Zheng, J. Hu, *Org. Lett.* **2011**, *13*, 5342-5345; b) M. Miele, R. D'Orsi, V. Sridharan, W. Holzer, V. Pace, *Chem. Commun.* **2019**, *55*, 12960-12963. The behavior of $TMSCF_3$ seems different from that of the difluoro-analogue ($TMSCHF_2$) which smootly delivers the corresponding CHF_2 anion in the presence of a tertiary alkoxide (KO*t*Pent), see: c) M. Miele, A. Citarella, N. Micale, W. Holzer, V. Pace, *Org. Lett.* **2019**, *21*, 8261-8265
[40] L. Castoldi, W. Holzer, T. Langer, V. Pace, *Chem. Commun.* **2017**, *53*, 9498-9501.

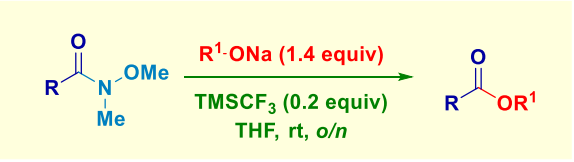
10.1002/adsc.202400008

COMMUNICATIONS

Ruppert-Prakash Reagent ($TMSCF_3$)-Catalyzed Chemoselective Esterification of Weinreb Amides

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Margherita Miele, Laura Castoldi, Egle Beccalli and Vittorio Pace*



- *57 examples*
- *high yielding*
- *direct procedure*
- *no racemization*
- *high chemoselectivity*
- *broad functional group tolerance*