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Reductive Alkylation of Amines with Carboxylic Ortho Esters

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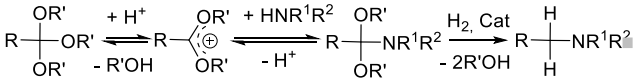
Abstract. We have demonstrated for the first time that carboxylic ortho esters could be used as an alkylating agent in the reductive alkylation of amines. A variety of amines, including amino acid esters, were alkylated affording mono-alkylated products with high selectivity in practical to high yields using standard heterogeneous catalysts. By applying acyclic ortho esters alkylation was completed at room temperature.

Keywords: Ortho esters; Amines; Alkylation; Hydrogenation; Heterogeneous catalysis

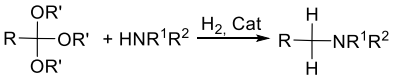
Amines are an interesting target in organic chemistry with great potential in the pharmaceutical and fine chemical industries. Reductive alkylation of ammonia, primary or secondary amines with carbonyl compounds constitutes one of the most convenient and practical approaches for synthesis of higher alkylated amines.[1] Using hydrogen as a reducing agent is one of the powerful methods for carrying out this transformation. Although diverse modifications have been established, the development of catalytic reduction with hydrogen continues to be one of the greatest tasks as many publications over the last few years show.[2] In the last years significant progress has been achieved in reductive alkylation of amines using alcohols[3, 4], carboxylic acids[4-8] and CO_2[9, 10] as alkylating agents. Despite the advances made by biocatalytic methods[4], by using borohydride[5, 7a] and silanes[6, 7] as reducing agents catalytic hydrogenation remains one of the major challenges.[7a, 8] Hence, the development of milder and more selective methods using commercially available heterogeneous catalysts is of significant interest for the fine chemical and pharmaceutical industries. Very recently, we have demonstrated that hydrogenolysis of the amide acetals and imido esters proceed at very mild conditions over commercially available hydrogenation catalysts.[11] Trialkyl orhto carboxylates react with primary and secondary amines in the presence of catalytic amounts of acid to yield an amide acetal (Scheme1).[12] Therefore, it appears likely that hydrogenation of a mixture of ortho esters and amines in the presence of catalytic amounts of an acid and hydrogenation catalyst should give an alkylated amine. In fact, the first experiments

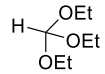
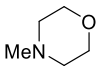
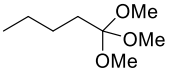
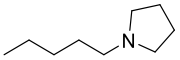
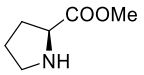
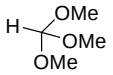
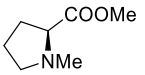
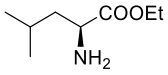
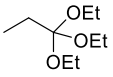
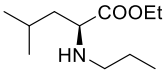


Scheme 1. Aminolysis of ortho esters and subsequent hydrogenolysis.

showed that commercially available morpholine (**1a**) and methyl orthoformate (**2a**) could be efficiently converted into N-methylmorpholine. Furthermore, the alkylation proceeded smoothly over almost every hydrogenation catalyst such as Pd/C, Pt/C, Ru/C and Rh/C. The hydrogen uptake finished in minutes at 110°C, 40 bar and using 5 mol% of p-toluenesulfonic acid and 1 mol% of powder catalyst affording the desired product in almost quantitative yield. As shown Table 1, pyrrolidine (**1b**) and methyl L-prolinate (**1c**) have been transformed into N-pentylpyrrolidine (**3b**) and methyl N-methyl-L-prolinate with very good to excellent yields (**3c**) over all four powder catalyst using this method. Also N-propyl-L-leucine ethyl ester (**3d**) was prepared in good yields with very good selectivity toward monoalkylation. The generality of this approach was proven by smooth alkylation of a number of primary and secondary amines, including aminoacids (Table 2). Remarkably, 3-pyrroline (**1j**), anilines (**1f-1h**) and amino acid esters (**1c**, **1d**, **1k-1n**) could be alkylated at room temperature by applying acyclic ortho esters. The alkylation of diethyl L-glutamate (**1m**) at 60°C is accompanied by intramolecular aminolysis with formation of lactam (**3o**). The alkylation of aniline (**1e**) with ethyl orthopropionate (**2d**) and pyrrolidine (**1b**) with ethyl orthobenzoate (**2e**) give synthetically useful to good yields at elevated temperatures. At these conditions, the alkylation of benzylamine (**1i**) gives dialkyated product (**3j**) in quantitative yields using 3 equivalents of ethyl orthoformate (**2a**), while mixture of mono- and dialkylation products formed by using one equivalent of ortho ester. Furthermore, alkylation of anilines (**1f-1h**) with ethyl orthoformate (**2a**) proceed smoothly at room temperature in presence of 5% Pt/C delivering the dialkylated products (**3f-3h**) in quantitative yields. We have shown that Pt/C catalyst in the alkylation of 3-chloroaniline (**1g**) was recyclable with no appreciable

Table 1. Catalyst screening in reductive alkylation.[a]



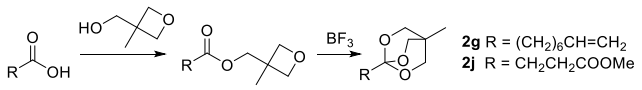
Amine		Ortho Etser		Product		Catalyst	Time[b], h	Yield[c], %
	1a		2a		3a	5% Pd/C	0.3	92
						5% Pt/C	0.2	97
						5% Ru/C	0.25	96
						5% RhC	0.25	98
	1b		2b		3b	5% Pd/C	0.8	81
						5% Pt/C	0.25	95
						5% Ru/C	0.25	90
						5% Rh/C	0.1	86
	1c		2c		3c	5% Pd/C	0.5	98
						5% Pt/C	0.15	99
						5% Ru/C	0.25	98
						5% Rh/C	0.25	97
	1d		2d		3d	5% Pd/C	1	82
						5% Pt/C	0.1	75
						5% Ru/C	0.6	71
						5% Rh/C	0.2	85

a) Conditions: amine (5 mmol), ortho ester (6 mmol), catalyst (1 mol%), pTSA (5 mol%), 5 mL MeOH or EtOH, 40 bar H_2, 110 °C. b) Time required for completeness of hydrogen uptake. c) Products were isolated as hydrochlorides and yields determined by GC analysis using tetradecane as an internal standard.

loss of activity for three repeated runs, indicating that the catalyst is not only reusable but also has high chemoselectivity toward alkylation. Applying Pd/C and Rh/C as catalysts in the alkylation of 3-chloroaniline (**1g**) and 4-bromoaniline (**1h**) led to predominant formation of cyclohexyldimethylamine - product of hydrodehalogenation and aromatic ring hydrogenation. By the alkylation of 4-bromoaniline (**1h**) using Pt/C noticeable amounts of N,N-dimethylaniline (product of hydrodehalogenation) were detected in the reaction mixture.

In general, the hydrogenation of carbon-carbon double bond is very rapid over the most hydrogenation catalysts.[1f] The simultaneous reduction of alkene units were observed at hydrogenolysis of amide acetals over Pt/C.[11b] As expected, also hydrogenation of double bonds in 3-pyrroline (**1j**) and ortho ester (**2g**) were observed by synthesis of amines (**3b** and **3p**).

Recently we have shown that hydrogenolysis of amideacetals proceed with high chemoselectity without racemization of the neighboring chiral center.[11] On the other site, amino-acids and their esters can be racemized under acidic conditions, although this requires strong acids and temperatures well above 100°C.[13] We were very surprised to learn that proline methyl ester (**1c**) racemizes in the presence of an equimolar HCl in MeOH at room temperature. In contrast, the racemization of alanine (**1k**), leucine (**1d**) and phenylalanine (**1l**) esters proceed at elevated temperatures (>100°C) in the presence of an equimolar HCl in alcohol as described in earlier studies.[13] It is therefore not surprising that alkylation of these amino acid esters at room temperature proceeds without racemization (see Supporting Information). Partial racemization occurs, however, by alkylation at 120°C at weak acidic conditions.



Scheme 2. Straightforward method for synthesis of bicyclic ortho esters.[14,15]

Many straightforward routes toward the preparation of ortho esters are the subject of numerous reviews.[12] The method outlined on Scheme 2 provides the general method for preparation of ortho esters direct from carboxylic acids. The latter method gives the facile access to a variety of bicyclic ortho esters with different substitution patterns.[14, 15] Generally, the reaction of bicyclic ortho esters and aminoacids proceeds smoothly at high temperature (100 °C) to give good overall yield of the desired product after hours by alkylation with 1-alkyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**2g**-**2i**). Even higher temperature (120 °C) and heating for days (48-72 h) are required for achieving good yields by alkylation with 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane-1-propanoic acid methyl ester (**2j**). The alkylation of methyl L-leucinate (**1p**) at 120°C is accompanied by intramolecular aminolysis with formation of lactam (**3s**). Nevertheless, these examples show practical usability of biciclyc ortho esters as alkylating agents

In conclusion, it was for the first time demonstrated that carboxylic ortho esters could be used as an alkylating agent in the reductive alkylation of amines. The present method is especially useful for selective monoalkylation of primary amines and methylation under water-free conditions. Furthermore, the developed method has several advantages, especially as off-the-shelf catalysts could be utilized. By applying acyclic ortho esters alkylation complete at room temperature.

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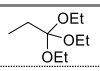
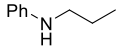
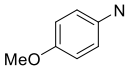
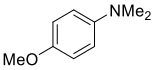
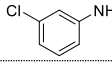
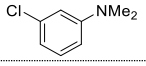
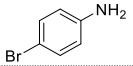
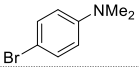
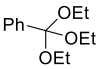
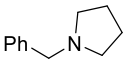
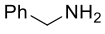
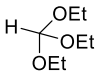
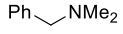
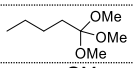
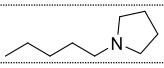
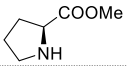
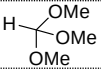
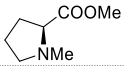
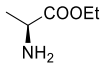
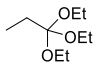
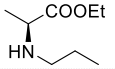
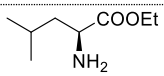
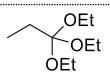
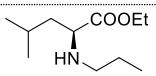
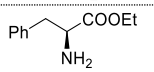
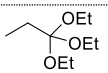
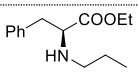
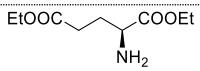
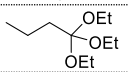
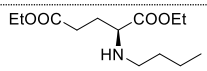
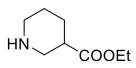
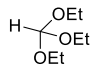
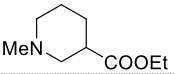
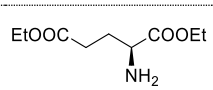
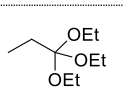
Table 2. Isolated yields in reductive alkylation with carboxylic ortho esters.[a]

Amine		Ortho Ester		Product		Catalyst	Temperature °C	Time[b] h	Yield[c] %
$PhNH_2$	1e		2d		3e	5% Pt/C pTSA	110	12	73[d]
	1f		2a		3f	5% Pt/C TFA	25	4	99[e]
						5% Rh/C TFA	25	4	99[e]
	1g		2a		3g	5% Pt/C TFA	25	4	99[e]
	1h		2a		3h	5% Pt/C TFA	25	4	65[e,f]
	1b		2e		3i	5% Pt/C pTSA	110	5	93
						5% Rh/C pTSA	110	8	81
	1i		2a		3j	5% Pd/C pTSA	110	14	99[e]
						5% Pt/C pTSA	110	1	99[e]
	1j		2b		3b	5% Pt/C TFA	25	24	86
	1c		2c		3c	5% Pt/C TFA	25	24	83[g]
	1k		2d		3k	5% Pt/C TFA	25	24	79[h]
	1d		2d		3d	5% Pt/C TFA	25	24	85[h]
	1l		2d		3l	5% Pt/C TFA	25	24	90[h]
	1m		2f		3m	5% Pt/C TFA	25	28	92[g]
	1n		2a		3n	5% Pt/C pTSA	25	24	90
	1m		2d		3o	5% Pt/C TFA	60	4	91[g]
	1b		2g		3p	5% Pt/C TFA	100	24	94
	1n		2h		3q	5% Pt/C pTSA	100	20	91
	1o		2i		3r	5% Pt/C pTSA	100	1	82[g]
	1q		2j		3s	5% Ru/C pTSA	120	48	90[g]
	1c		2j		3t	5% Ru/C pTSA	120	56	82[g]
	1q		2j		3u	12% Pt/C pTSA	120	72	70
	1n		2j		3v	12% Pt/C pTSA	120	48	45

a) Conditions: amine (0.1 mol), ortho ester (0.12 mol), catalyst (0.5 mol%), pTSA or TFA (5 mol%), 30 mL MeOH or EtOH, 40 bar H_2. b) Time required for completeness of hydrogen uptake. c) Products were isolated by distillation in vacuum or by column chromatography (see Supporting Information). d) 11% of $PhN(n\text{-}Pr)_2$ and 4% of EtCONHPh were detected in crude product after hydrogenation. e) 3 Equivalents of orthoformate was used; f) 30% of N,N-dimethylaniline were detected in crude product after hydrogenation. g) The substrate was enantiomerically pure (>97% e.e.), the product possesses a significant optical activity but the e.e. has not been determined. h) E.e. > 98% determined by integration of ^{19}F NMR signals and GC peaks of MTPA amides.

Experimental Section

A 100 ml autoclave was charged with catalyst (0.5 mol%) and closed, autoclave repeatedly purged with nitrogen, then a solution of amine (0.1 mol) and ortho ester (0.12 mmol in 30 ml of dry methanol/ethanol and freshly prepared water-free solution of p-toluenesulfonic acid in methanol (ethanol) (5 mmol) or trifluoroacetic acid (0.57 g, 5 mmol) were added using syringe under nitrogen. The autoclave was heated to desired temperature and pressurized to 40 bar with hydrogen. After hydrogen uptake cased, autoclave was allowed to cool down to ambient temperature and depressurized, the catalyst was filtered through celite, solids washed with methanol/ethanol, combined filtrates concentrated on rotary evaporator and dissolved in 50 ml of 2N hydrochloric acid (cold) and washed with diethyl ether. The aqueous layer was basified with 2N NaOH and extracted with diethyl ether. Combined organic layers were dried over K_2CO_3 and distilled in vacuum or purified by column chromatography.

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References

[1] For reviews on catalytic reductive amination of carbonyl compounds, see: a) W. S. Emerson, *Org. React*. **1948**, *4*, 174-255; b) M. Freifelder, *Practical Catalytic Hydrogenation*, Wiley, New York, **1971**, pp. 238-260; c) M. V. Klyuev, M. L. Khidekel, *Russ. Chem. Rev*. **1980**, *49*, 14-27; d) P. N. Rylander, *Hydrogenation Methods*, Academic Press, London, **1985**, pp. 94-103; e) V. A. Tarasevich, N. G. Kozlov, *Russ. Chem. Rev*. **1999**, *68*, 55; f) S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, John Wiley & Sons, Inc. N.Y.; **2001**, pp. 226-253; g) S. Gomez, J. A Peters, T. Maschmeyer, *Adv. Synth.Catal.* **2002**, *344*, 1037-1057; h) V. I. Tararov, A. Börner, *Synlett* **2005**, 203–211; i) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal*. **2010**, *352*, 753-819; j) C. Wang, J. Xiao, *Top. Curr. Chem*. **2014**, *343*, 261-282; k) K. N. Gusak, Zh. V. Ignatovich, E. V. Koroleva, *Russ. Chem. Rev*. **2015**, *84*, 288–309; l) H. Alinezhad, H. Yavari, F. Salehian, *Curr. Org. Chem*. **2015**, *19*, 1021–1049.

[2] For very recent examples of catalytic reductive amination of carbonyl compounds, see: a) Y. Chen, Y-M. He, S. Zhang, T. Miao, Q-H. Fan, *Angew. Chem.* **2019**, *131*, 3849-3853; *Angew. Chem. Int. Ed*. **2019**, *58*, 3809-3813; b) D. Wei, A. Bruneau-Voisine, D. A. Valyaev, N. Lugan, J.-B. Sortais, *Chem. Commun*. **2018**, *54*, 4302-4305; c) Y. Hoshimoto, T. Kinoshita, S. Hazra, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2018**, *140*, 7292−7300; d) F. Christie, A. Zanotti-Gerosa, D. Grainger, *ChemCatChem* **2018**, *10*, 1012–1018; e) J. S. Sapsford, D. J. Scott, N. J. Allcock, M. J. Fuchter, C. J. Tighe, A. E. Ashley, *Adv. Synth. Catal.* **2018**, *360*, 1066–1071; f) T. Senthamarai, K. Murugesan, J. Schneidewind, N. V. Kalevaru, W. Baumann, H. Neumann, P. C. J. Kamer, M. Beller, R. V. Jagadeesh, *Nature Commun.* **2018**, 4123-4135; g) T. Senthamarai, K. Murugesan, K. Natte, N. V. Kalevaru, H. Neumann, P.C.J. Kamer, R.V. Jagadeesh, *ChemCatChem* **2018**, *10*, 1235–1240; h) Z. Pan, L. Shen, D. Song, Z. Xie, F. Ling, W. Zhong, *J. Org. Chem.* **2018**, *83*, 11502−11509; i) M. S. Thakur, O. S. Nayal, A. Sharma, R. Rana, N. Kumar, S. K. Maurya, *Eur. J. Org. Chem.* **2018**, 6729–6732; j) B. Li, S. Liu, M. Wu, Q. Lin, W. Deng, S. Jiang, L. Chen, *Tetrahedron Lett.* **2018**, *59*, 3467–3472; k) J. Gallardo-Donaire, M. Hermsen, J. Wysocki, M. Ernst, F. Rominger, O. Trapp, A. S. K. Hashmi, A. Schäfer, P. Comba, T. Schaub, *J. Am. Chem. Soc*. **2018**, *140*, 355−361; l) X. Tan, S. Gao, W. Zeng, S. Xin, Q. Yin, X. Zhang, *J. Am. Chem. Soc*. **2018,** *140*, 2024−2027; m) Q.-H. Li, Y. Dong, F.-F. Chen, L. Liu, C.-X. Li, J.-H. Xu, G.-W. Zheng, *Chinese J. Cat*. **2018**, *39*, 1625–1632; n) Y. S. E. Varjosaari, V. Skrypai, F. Suating, J. J. M. Hurley, A. M. De Lio, T. M. Gilbert, M. J. Adler, *Adv. Synth. Catal*. **2017**, *359*, 1872–1878; o) S. Wang, H. Huang, C. Bruneau, C. Fischmeister, *ChemSusChem* **2017**, *10*, 4150–4154; p) Z. O. S. Nayal, M. S. Thakur, V. Bhatt, M. Kumar, N. Kumar, B. Singh, U. Sharma, *Chem. Commun*. **2016**, *52*, 9648–9651.

[3] a) Y. Wang, S. Furukawa, X. Fu, N. Yan, *ACS Catal.* **2020**, *10*, 311-335; b) K. Das, A.l Kumar, A. Jana, B. Maji, *Inorg. Chim. Acta*, **2020**, *502*, 119358; c) Y. Long, P. Wang, Y. Fei, D. Zhou, S. Liu, Y. Deng, *Green Chem.* **2019**, *21*, 141-148; d) D. Wei, O. Sadek, V. Dorcet, T. Roisnel, C. Darcel, E. Gras, E. Clot, J.-B Sortais, *J. Catal.*, **2018**, *366*, 300-309; e) J. J. A. Celaje, X. Zhang, F. Zhang, L. Kam, J. R. Herron, T. J Williams, *ACS Catal*. **2017**, *7*, 1136-1142; f) X.-J. Yu, H.-Y. He, L. Yang, H.-Y. Fu, X.-L. Zheng, H. Chen R.-X. Li, *Catal. Commun*. **2017**, *95*, 54-57; g) R. Mamidala, V. Mukundam, K. Dhanunjayarao, K. Venkatasubbaiah, *Tetrahedron* **2017**, *73*, 2225-2233; h) N. Nakagawa, E. J. Derrah, M. Schelwies, F. Rominger, O. Trapp, T. Schaub, *Dalt. Trans.* **2016**, *45*, 6856-6865; i) S. Elangovan, J. Neumann, J.-B. Sortais, K. Junge, C. Darcel, M. Beller, *Nat. Commun*. **2016**, *7*, 12641; j) Q. Yang, Q. Wang, Z. Yu, *Chem. Soc. Rev*. **2015**, *44*, 2305-2329; k) G. Guillena, D. Ramon, M. Yus, *Chem. Rev*. **2010**, *110*, 1611-1641.

[4] J. Ramsden, R. S. Heath, S. Derrington, S. L. Montgomery, J. Mangas-Sanchez, K. R. Mulholland, N. J. Turner, *J. Am. Chem. Soc.* **2019**, *141*, 1201-1206.

[5] a) Y. Wei, Q. Xuan, Y. Zhou, Q. Song, *Org. Chem. Front*. **2018**, *5*, 3510-3514; b) S. A. I. Quadri, T. C. Das, S. Jadhav, M. Farooqui, *Synth. Commun*. **2018**, *48*, 267–277.

[6] a) C. Qiao, X.-Y. Yao, X.-F. Liu, H.-R. Li, L.-N. He, *Asian J. Org. Chem*. **2018**, *7*, 1815–1818; b) M.-Y. Wang, N. Wang, X.-F. Liu, C. Qiao, L.-N. He, *Green Chem.* **2018**, *20*, 1564-1570; c) K. G. Andrews, R. Faizova, R. M. Denton, *Nat. Commun.* **2017**, *8*, 15913; d) K. G. Andrews, D. M. Summers, L. J. Donnelly, R. M. Denton, *Chem. Commun*. **2016**, *52*, 1855–1858; e) C. Qiao, X.-F. Liu, X. Liu, L.-N. He, *Org. Lett*. **2017**, *19*,

1490–1493; f) Y. Ogiwara, T. Uchiyama, N. Sakai, *Angew. Chem*. **2016**, *128*, 1896–1899; *Angew. Chem. Int. Ed*. **2016**, *55*, 1864–1867; g) M.-C. Fu, R. Shang, W.-M. Cheng, Y. Fu, *Angew. Chem*. **2015**, *127*, 9170–9174; *Angew. Chem. Int. Ed*. **2015**, *54*, 9042–9046; h) I. Sorribes, K. Junge, M. Beller, *J. Am. Chem. Soc*. **2014**, *136*, 14314–14319; i) I. Sorribes, K. Junge, M. Beller, *Chem. Eur. J*. **2014**, *20*, 7878–7883.

[7] a) J. R. Cabrero-Antonino, R. Adam, M. Beller, *Angew. Chem*. **2019**, *131*, 12950-12968; *Angew. Chem., Int. Ed*., **2019**, *58*, 12820-12838; b) Y. Hoshimoto, S. Ogoshi, *ACS Catal.* **2019**, *9*, 5439-5444.

[8] For examples of catalytic reductive N-alkylation of amines with acids using hydrogen as reducing agent, see: a) T. Toyao, K. W. Ting, S. M. A. H. Siddiki, A. S. Touchy, W. Onodera, Z. Maeno, H. Ariga-Miwa, Y. Kanda, K. Asakura, K.-ichi Shimizu, *Catal. Sci. Technol.* **201**9, *9*, 5413-5424; b) W.-D. Li, D.-Y. Zhu, G. Li, J. Chen, J.-B. Xia, *Adv. Synth. Catal.* **2019,** *361*, 5098-5104; c) W. Liu, B. Sahoo, A. Spannenberg, K. Junge, M. Beller, *Angew. Chem.* **2018**, *130*, 11847–11851; *Angew. Chem. Int. Ed*. **2018**, *57*, 11673–11677; d) B. Emayavaramban, P. Chakraborty, B. Sundararaju, *ChemSusChem* **2018**, *11*, 3089-3093; e) T. Toyao, S. M. A. H. Siddiki, Y. Morita, T. Kamachi, A. S. Touchy, W. Onodera, K. Kon, S. Furukawa, H. Ariga, K. Asakura, K. Yoshizawa, K. Shimizu, *Chem. Eur. J*. **2017**, *23*, 14848-14859; f) Y. Shi, P. C. J. Kamer, D. J. Cole-Hamilton, *Green Chem*. **2017**, *19*, 5460–5466; g) I. Sorribes, J. R. Cabrero-Antonino, C. Vicent, K. Junge, M. Beller, *J. Am. Chem. Soc*. **2015**, *137*, 13580–13587.

[9] For examples of catalytic reductive N-methylation of amines with CO_2 using hydrogen as reducing agent, see a) K. Liu, Z. Zhao, W. Lin, Q. Liu, Q. Wu, R. Shi, C. Zhang, H. Cheng, M. Arai, F. Zhao, *ChemCatChem* **2019**, *11*, 3919-3926; b) T. Toyao, S. M. A. H. Siddiki, K. Kon, K.-ichi Shimizu, *Chem. Rec*. **2018**, *18*, 1374-1393; c) T. Toyao, S. M. A. H. Siddiki, Y. Morita, T. Kamachi, A. S. Touchy, W. Onodera, K. Kon, S. Furukawa, H. Ariga, K. Asakura, K. Yoshizawa, K. I. Shimizu, *Chem. Eur. J*. **2017**, *23*, 14848-14859.

[10] For reviews, see: a) M. Hulla, P. J. Dyson, *Angew. Chem.* **2020** 59, 1002-1017; *Angew. Chem. Int. Ed.* **2020**, *59*, 1002-1017; b) J.-Y. Li, Q.-W. Song, K. Zhang, P. Liu, *Molecules* **2019**, *24*, 182; c) Y. Yang, J.-W. Lee, *Chem. Sci.* **2019**, *10*, 3905-3926; d) K. Beydoun, J. Klankermayer in *Organometallics for Green Catalysis* (Eds.: P. Dixneuf, J. F. Soulé) *Top. Organomet. Chem*. **2018**, *63*, 39-76.

[11] R. Kadyrov, *ChemCatChem* **2018**, *10*, 170-172; b) R. Kadyrov, *Adv. Synt. Cat.* **2019**, *361*, 185–191.

[12] a) R. H. DeWolfe, *Carboxylic ortho acid derivatives*, Academic Press, NY, **1970**, pp. 178-222; b) H. Meerwein in *Methoden Org. Chem*. (Houben-Weyl), Band 6/3, (Ed.: J. Falbe) Thieme, Stuttgart, **1985**, pp. 299-324; c) G. Simchen in *Methoden Org. Chem*. (Houben-Weyl), Band E5/1, (Ed.: J. Falbe) Thieme, Stuttgart, **1985**, pp. 105-122; d) W. Kantlehner in *Science of Synthesis* Vol. 22, (Ed.: A. B. Charette) Thieme; Stuttgart; 2005, pp. 795-842.

[13] a) S. Yamada, C. Hongo, R. Yoshioka, I. Chibata, *J. Org. Chem.* **1983**, *48*, 843-846; b) R. Baum, G. G. Smith, *J. Am. Chem. Soc*. **1986**, *108*, 7325-7327; c) E. J. Ebbers, G. J. A. Ariaans, J. P. M. Houbiers, A. Bruggink, B. Zwanenburg, *Tetrahedron*, **1997**, *53*, 9417-9476.

[14] a) H. Lebel, M. Grenon in *Science of Synthesis* Vol. 22. (Ed.: A. B. Charette) Thieme; Stuttgart; 2005, pp. 669-747; b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*. 3rd ed.; Wiley: New York, **1999**, pp 437–440; c) W. Kantlehner in *Comprehensive Organic Synthesis*, Vol 6 (Eds: B. M. Trost and I. Fleming), Pergamon, Oxford, **1991**, pp. 556-599; d) R. H. DeWolfe, *Synthesis* **1974**, 153-172.

[15] a) E. J. Corey, N. Raju, *Tetrahedron Lett*. **1983**, *24*, 5571–5574; b) J. D. Winkler, R. D. Scott, P. G. Williard, *J. Am. Chem. Soc*. **1990**, *112*, 8971-8975; c) K. Rakus, S. P. Verevkin, W.-H. Peng, H.-D. Beckhaus, C. Riichardt, *Liebigs Ann*. **1995**, 2059-2067; c) S. Kanoh, M. Naka, T. Nishimura, M. Motoi, *Tetrahedron* **2002**, *58*, 7049–7064; d) J. M. Andre´s, N. de Elena, R. Pedrosa, *Tetrahedron* **2000**, *56*, 1523–1531; e) N. G. W. Rose, *Tetrahedron* **2001**, *57*, 1497-1507; f) M. A. Letavic, C. H. Yu, *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3243–3246; g) D. B. Hansen, M. M. Joullie, *Tetrahedron: Asymmetry* **2005**, *16*, 3963–3969; h) D. B. Hansen, X. Wan, P. J. Carroll, M. M. Joullie, *J. Org. Chem.* **2005**, *70*, 3120-3126; i) A. G. Zhdanko, V. G Nenajdenko *J. Org. Chem.* **2009**, *74*, 884–887; j) J. Jeon, S.-H. Kim, J. H. Lee, J. S. Oh, D. Y. Park, Y. G Kim, *Bull. Korean Chem. Soc*. **2009**, *30*, 1003-1008; k) A. G. Zhdanko, A. V. Gulevich, V. G. Nenajdenko *Tetrahedron* **2009**, *65*, 4692-4702; l) N. Choony, L. James, C. Rabun, *Synth. Commun*. **2011**, *41*, 2539-2543; m) X. Liang, C.-J. Lee, J. Zhao, E. J. Toone, P. Zhou, *J. Med. Chem*. **2013**, *56*, 6954−6966; n) M. J. Di Maso, M. A. St. Peter, J. T. Shaw, *Org. Syntheses* **2015**, *92*, 328-341; o) C. Adamson, R. J. Pengelly, S. Shamsi Kazem Abadi, S. Chakladar, J. Draper, R. Britton, T. M. Gloster, A. J. Bennet, *Angew. Chem*. **2016,** *128*, 15202–15206; *Angew. Chem., Int. Ed*. **2016**, *55*, 14978-14982; p) D. Przybyla, U. Nubbemeyer, *Synthesis* **2017**, *49*, 770-774; q) L. Qian, C.-J. Zhang, J. Wu, S. Q. Yao, *Chem. Eur. J*. **2017**, *23*, 360-369; r) D. P. Zarezin, O. I. Shmatova, V. G. Nenajdenko, *Mendeleev Commun*. **2018**, *28*, 364-365.

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Reductive Alkylation of Amines with Carboxylic Ortho Esters

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