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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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$Me_2(CH_2Cl)SiCN$: Bifunctional Cyanating Reagent for the Synthesis of Tertiary Alcohols with a Chloromethyl Ketone Moiety via Ketone Cyanosilylation

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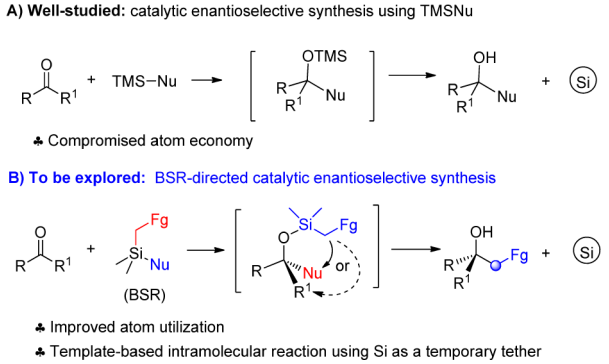
Supporting Information

ABSTRACT: We report a novel bifunctional cyanating reagent, $Me_2(CH_2Cl)SiCN$, which paves the way to a one-pot sequential synthesis of tertiary alcohols featuring a chloromethyl ketone moiety via enantioselective ketone cyanosilylation. This method contributes to gram-scale enantioselective total synthesis of the aggregation pheromone of the Colorado potato beetle, (*S*)-CPB.

Trimethylsilyl nucleophiles (TMSNu)[1] play an important role in developing enantioselective addition reactions to carbonyl compounds. Such reactions are important for the preparation of optically active alcohol derivatives.[1,2] The application of TMSNu is particularly helpful when the corresponding pronucleophiles are inconvenient to handle or are difficult to activate by deprotonation under mild conditions. However, despite their many advantages, the use of TMSNu reagents inevitably leads to compromised atom economy.[3] This is because the TMS group is usually not a part of the final product, although it may serve as an alcohol protecting group for further transformations (Scheme 1A).

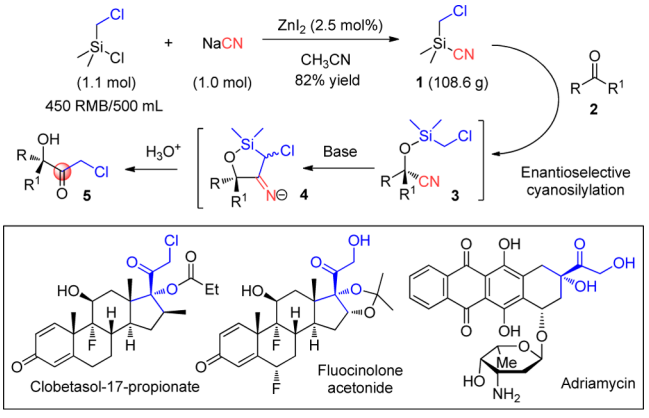
Scheme 1. Working Hypothesis



In view of this deficiency, along with our interest in silicon-mediated synthesis,[4] we consider developing bifunctional silyl reagents (BSR) for enantioselective catalytic synthesis (Scheme 1B). A characteristic feature of BSR, compared with traditional TMSNu, is that a methyl group on the silicon is replaced by a functionalized group. Enantioselective catalytic carbonyl addition reactions using BSR will afford adducts with the silicon as a temporary tether,[5] which unifies a pair of functional groups: one on the silicon and the other on the stereocenter (the Nu or a pre-existing functionality R^1). Under suitable conditions, a further template-based intramolecular reaction transfers the functional group on the silicon to the final product. This not only increases the atom utilization of the synthesis but also enables a transformation that may otherwise be difficult to achieve in an intermolecular fashion.

To demonstrate the feasibility of this concept, we first designed a bifunctional cyanating reagent **1**, based on our efforts in the ketone cyanosilylation.[4a,b] Reagent **1** can be easily obtained from cheap $Me_2(CH_2Cl)SiCl$ and NaCN on a mole scale (Scheme 2). An attractive feature of reagent **1** is that, when

Scheme 2. Synthesis and Application of BSR 1



applied to ketone cyanosilylation, the chloromethyl group of the resulting chiral cyanohydrins **3** may react with the cyano group to afford intermediate **4** upon treating with base.[6] A further hydrolysis then affords tertiary alcohols **5** featuring a chloromethyl ketone moiety, which is a prominent structural motif present in drugs and bioactive compounds,[7] as well as a versatile building block for complex-generating synthesis.

With bifunctional cyanating reagent **1** in hand, we first examined its performance in the ketone cyanosilylation catalyzed

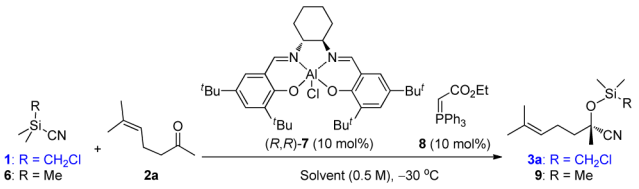
Received: June 1, 2016
Published: July 11, 2016

DOI: 10.1021/jacs.6b05601
J. Am. Chem. Soc. 2016, 138, 8730–8733

by the merger of chiral (salen)AlCl[8] complex **7** and phosphorane **8**, which we recently discovered for highly enantioselective ketone cyanosilylation using trimethylsilyl cyanide (TMSCN) **6**.[4a]

Notably, compared with TMSCN, our bifunctional reagent **1** exhibited improved properties (Table 1). When using CH_2Cl_2 as

Table 1. Comparison of $Me_2(CH_2Cl)SiCN$ and TMSCN[a]



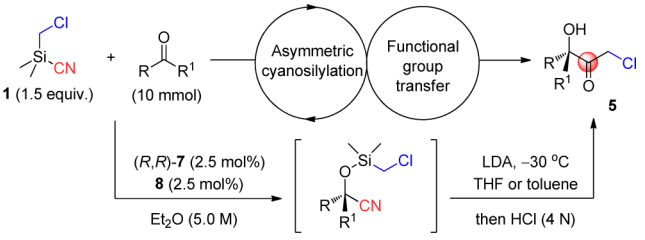
Entry	Solvent	**3a**: R = CH_2Cl			**9**: R = CH_3		
		Time (h)	Yield (%)[b]	Ee (%)[c]	Time (h)	Yield (%)[b]	Ee (%)[c]
1	CH_2Cl_2	36	30	92	36	trace	95
2	EtOAc	36	92	96	48	77	84
3	THF	10	97	97	33	92	96
4	Et_2O	2	94	97	19	86	96
5	i-Pr_2O	2	94	97	19	89	95
6	t-BuOMe	3	93	96	19	90	95
7	toluene	48	61	94	28	80	96
8	n-hexane	22	93	82	22	90	93
9	DMF	48	n.r.	--	48	90	91

[a]Reactions were run using 0.5 mmol of **3a** and 2.0 equiv of reagent **1** or **6**. [b]Isolated yield. [c]Determined by chiral HPLC analysis of free cyanohydrin.

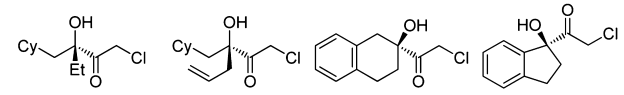
the solvent at −30 °C, ketone **2a** reacted with **1** to afford the adduct **3a** in 30% yield; however, the reaction using TMSCN gave only a trace amount of product (entry 1). The reactivity was greatly increased when ethyl acetate and ethers were used as solvent (entries 2−6). In particular, the cyanosilylation of **2a** and **1** in Et_2O was completed in only 2 h, to afford **3a** in 94% yield with 97% ee (entry 4). In ether solvents, reagent **1** exhibited much higher reactivity than TMSCN; although satisfactory results for product **9** were also obtained (entries 3−6). In contrast, when toluene, n-hexane, or DMF was used as solvent, reagent **1** was less active than TMSCN. No reaction of **1** and **2a** took place in DMF (entries 7−9). These results imply that, under certain conditions, BSR might be more active than the corresponding TMSNu.

Having established the conditions for enantioselective cyanosilylation using reagent **1**, a one-pot synthesis of tertiary alcohols **5** was then developed. This was done to demonstrate the power of our new reagent **1** (Table 2). The cyanosilylation was run on a 10.0 or 20.0 mmol scale, in the presence of (*R*,*R*)-**7** and **8** (each 1−2.5 mol %). On completion of the initial step, the solvent and excess reagent **1** were removed under reduced pressure. THF or toluene (in the case of aryl ketones) was then added at −30 °C, followed by the addition of 1.5 equiv lithium diisopropylamide (LDA). By using such a convenient one-pot procedure, a variety of tertiary alcohols **5a**−**h**, featuring a chloromethyl ketone moiety, were readily prepared in good yields with excellent ee values (91−98%). Vinyl-, ethyl-, and allyl-substituted ketones also readily afforded the desired tertiary

Table 2. One-Pot Synthesis of Tertiary Alcohol 5



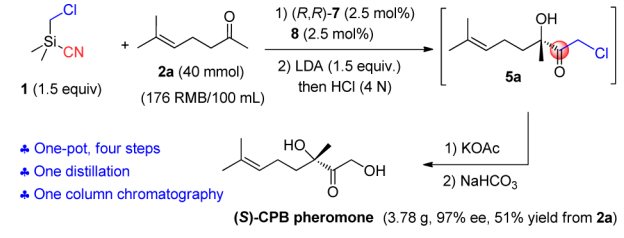
Entry	**Ketone**: R, R^1	**5**	Yield (%)[a]	Ee (%)[b]
1	**2a**: Me_2C=$CH(CH_2)_2$, Me	**5a**	66	97
2[c]	**2b**: Et, Me	**5b**	70	91
3	**2c**: n-C_5H_{11}, Me	**5c**	62	96
4[d]	**2d**: $BnCH_2$, Me	**5d**	60	98
5	**2e**: p-$OMeC_6H_4CH_2$, Me	**5e**	58	97
6[c]	**2f**: i-Pr, Me	**5f**	56	96
7	**2g**: p-$CF_3C_6H_4$, Me	**5g**	54	96
8	**2h**: p-ClC_6H_4, Me	**5h**	43	94
9	**10a**: Cyclohexyl, Vinyl	**5i**	59	94



[a]Isolated yield. [b]Determined by chiral HPLC analysis. [c]On a 20 mol scale. [d]1 mol % (*R*,*R*)-**7** and **8** was used for step 1.

alcohols **5i**−**k** in high to excellent ee values. Interestingly, cyclic ketones were also viable substrates for this protocol, as shown by the synthesis of products **5l** and **5m**[9] in good yield and high ee values.

This protocol was then applied to the enantioselective total synthesis of the pheromone of the Colorado potato beetle (CPB), which is potentially useful in integrated pest management programs.[10] Starting from 40 mmol ketone **2a** and 1.5 equiv of reagent **1**, tertiary alcohol **5a** was obtained and used directly for the following substitution and hydrolysis step, affording (*S*)-CPB pheromone in 51% yield (3.78 g) with 97% ee. However, although we used a variety of intermolecular transformations to convert cyanohydrin **9** to (*S*)-CPB pheromone, we were unsuccessful (details in section 4 of SI). This further supports our working hypothesis that it is possible to use BSR to develop a synthesis that is otherwise difficult to realize via intermolecular reactions.

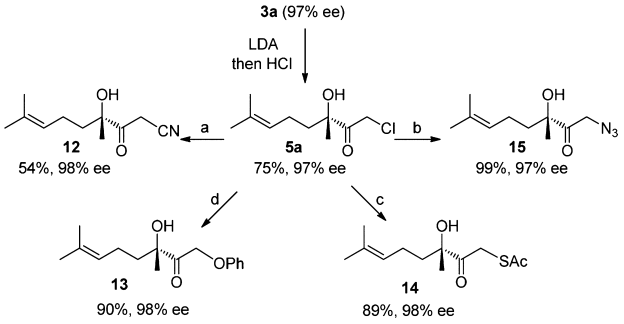


The highly efficient one-pot, four-step synthesis of (*S*)-CPB pheromone was very impressive, as only one column chromatography purification was involved. Because of the potential use of (*S*)-CPB, several synthetic routes have been

DOI: 10.1021/jacs.6b05601
J. Am. Chem. Soc. 2016, 138, 8730−8733

reported;[11] however, all involve several column chromatography purification steps. Our method is not only the shortest route but also the most practical method in terms of costs for substrate, reagents, chiral catalyst, and purification.

Due to the presence of a chloromethyl ketone moiety, the thus obtained tertiary alcohols **5** are versatile building blocks, as evidenced by the facile diversification of **5a**, which was readily obtained in 75% yield from isolated adduct **3a**. Carbon-, oxygen-, sulfur-, and nitrogen-based nucleophiles could all be readily introduced via substitution reactions, affording the corresponding products **12**−**15** in good yields, without the erosion of enantioselectivity.



Condition: a) NaCN, NaI, DMF; b) NaN_3, MeCN; c) KSAc, MeCN; d) PhOH, K_2CO_3, MeCN

The excellent ee values shown in Table 2 imply that reagent **1** paves the way for the highly enantioselective synthesis of cyanohydrins from a wide range of ketones. Despite significant advances having been made, highly enantioselective cyanosilylation of aliphatic ketones and α,β-unsaturated ketones is still very limited and highly desirable.[12] In the light of this, we examined the scope of ketone cyanosilylation using reagent **1** (Table 3).

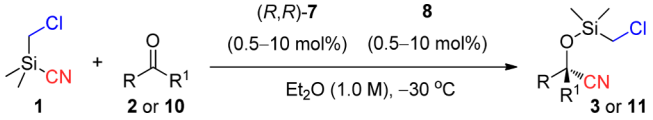
To our delight, differently substituted aliphatic ketones **2a**−**f** and **2i**−**o** afforded the desired products **3a**−**f** and **3i**−**o** in high to excellent yield with 91−98% ee (entries 1−6 and 9−12). Even 2-butanone **2b** gave the corresponding product **3b** with 91% ee (entry 2). Furthermore, the catalyst loading could be reduced to 0.5 mol %, as exemplified by the synthesis of product **3f** on a 50 mmol scale (entry 6). Aryl-substituted ketones **2g**,**h** and **2p**−**s** also worked well to afford the desired products with excellent ee values (entries 7, 8 and 16−19).

To our knowledge, these results represent the highest ee values for the cyanosilylation of linear aliphatic ketones. In the corresponding reaction using TMSCN, only one protocol using a three-component catalyst system consisting of (salen)-AlCl complex, phosphorane, and Ph_3PO could achieve 90−94% ee.[4a] Our new protocol based on $Me_2(CH_2Cl)SiCN$ is obviously superior because the enantioselectivities of the adducts **3a**−**f** and **3i**−**o** are better (>95% in most cases), and the catalyst system is simpler, as the use of cocatalyst Ph_3PO was unnecessary when using ether as the solvent. Nevertheless, it is still possible to activate reagent **1** by Ph_3PO for the cyanosilylation of less active ketones, as shown in the synthesis of tertiary alcohol **5m** (Table 1).[9]

An unprecedented highly enantioselective cyanosilylation of vinyl or ethynyl ketones **10a**−**g** was also developed, affording the desired cyanohydrins **11a**−**g** bearing a vinyl or ethynyl group at the tetrasubstituted carbon stereocenter in 83−97% ee (entries 20−26).

The synthetic value of this highly enantioselective method was exhibited by the greatly simplified synthesis of diol **16** in 53% overall yield with 97% ee in three steps from the inexpensive

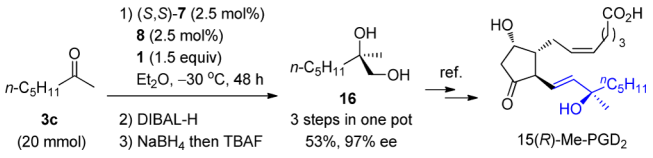
Table 3. Scope of Enantioselective Cyanosilylation[a]



Entry	Ketone	R	R^1	Product	Yield (%)[b]	Ee (%)[c]
1	**2a**	$Me_2C{=}CH(CH_2)_2$	Me	**3a**	94	97
2	**2b**	Et	Me	**3b**	94	91
3	**2c**	n-C_5H_{11}	Me	**3c**	92	96
4	**2d**	$BnCH_2$	Me	**3d**	87	98
5	**2e**	p-$MeOC_6H_4CH_2$	Me	**3e**	75	97
6[d]	**2f**	i-Pr	Me	**3f**	88	96
7[e]	**2g**	p-$CF_3C_6H_4$	Me	**3g**	89	95
8[e]	**2h**	p-ClC_6H_4	Me	**3h**	97	94
9	**2i**	i-$PrCH_2CH_2$	Me	**3i**	97	97
10	**2j**	(*E*)-$PhCH{=}CH(CH_2)_2$	Me	**3j**	96	94
11	**2k**	4-$FC_6H_4CH_2$	Me	**3k**	88	97
12	**2l**	2-$BrC_6H_4CH_2$	Me	**3l**	83	97
13	**2m**	Cyclohexyl	Me	**3m**	98	98
14	**2n**	Cyclohexyl	Et	**3n**	95	96
15	**2o**	Cyclohexyl	Allyl	**3o**	97	97
16[e]	**2p**	4-BrC_6H_4	Me	**3p**	98	94
17[e]	**2q**	4-$NO_2C_6H_4$	Me	**3q**	98	97
18[e]	**2r**	3-ClC_6H_4	Me	**3r**	99	90
19[e]	**2s**	2-Naphthyl	Me	**3s**	97	92
20	**10a**	Cyclohexyl	Vinyl	**11a**	98	94
21	**10b**	Cyclopentyl	Vinyl	**11b**	97	97
22[f]	**10c**	3-Cyclopentenyl	Vinyl	**11c**	98	91
23[f]	**10d**	$BnCH_2$	Vinyl	**11d**	88	83
24[f]	**10e**	(1-Cyclohexenyl)CH_2	Vinyl	**11e**	93	91
25[f]	**10f**	Cyclohexyl	Ethynyl	**11f**	90	89
26[f]	**10g**	$BnCH_2$	Ethynyl	**11g**	72	90

[a]See SI for details. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]On a 50 mmol scale in 5 mL Et_2O using 0.5 mol % (*S*,*S*)-**7** and **8**. [e]At −40 °C. [f]At −50 °C.

ketone **3c** ($66/1 kg, Sigma-Aldrich). As the key synthon to 15(*R*)-Me-PGD_2, a potent selective DP_2-receptor agonist, diol **16** was previously prepared in eight steps from very expensive (*R*)-(−)-citramalic acid ($125/250 mg, Sigma-Aldrich).[13]



In summary, we have proposed and demonstrated the advantages of using bifunctional silyl reagents for catalytic enantioselective carbonyl addition reactions. Accordingly, a bifunctional cyanating reagent, $Me_2(CH_2Cl)SiCN$, is developed for the highly enantioselective one-pot synthesis of tertiary alcohols with a chloromethyl ketone moiety via cyanosilylation. This reagent also contributes the best results to date in the cyanosilylation of aliphatic ketones and vinyl or ethynyl

DOI: 10.1021/jacs.6b05601
J. Am. Chem. Soc. 2016, 138, 8730−8733

ketones.[12] The application of reagent **1** and the development of other types of BSR are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05601.

Experimental details and data (PDF)
NMR spectra and HPLC traces for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank financial support from 973 program (2015CB856600), NSFC (21472049), and STCSM (168014339).

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(9) The cyanosilylation of 1-indanone using reagent **1** was run in CH_2Cl_2 at 0 °C, using 10 mol% (1*R*,2*R*)-1,2-diphenylethylenediamine derived (salen)AlCl, 10 mol% ylide **8**, and 50 mol% Ph_3PO. For details, see section 3 of SI.

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DOI: 10.1021/jacs.6b05601
J. Am. Chem. Soc. 2016, 138, 8730−8733