Application of Organocerium Reagents for the Efficient Conversion of *Z*-α,β-Unsaturated Weinreb Amides to *Z*-α,β-Unsaturated Ketones

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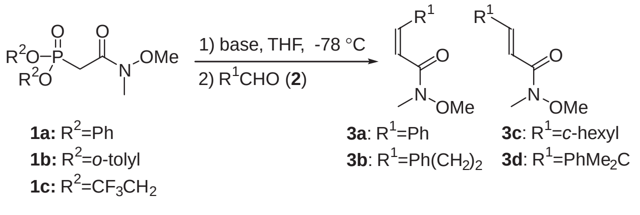
The reactions of *Z*-rich unsaturated Weinreb amides with organolithium and organocerium reagents were examined. Taking in consideration both the extent of geometry retention and cleanness of the reaction, organocerium reagents were more effective for the conversion to *Z*-α,β-unsaturated ketones.

The conjugated carbonyl unit is a versatile building block, and the geometry of the double bond often dictates the stereochemical outcome of reactions to this unit. For the less available *Z*-olefins, however, only a limited number of practical methods which accompany carbon–carbon double bond formation have been reported.[1–5] As for *Z*-α,β-unsaturated ketones, there is only one that can be coined general, and it only deals with methyl ketones.[4] In order to gain access to a wider range of *Z*-α,β-unsaturated ketones, we figured that utilization of α,β-unsaturated Weinreb amides might be practical.[6] That is, the use of a Wittig-type reaction to prepare *Z*-α,β-unsaturated Weinreb amides and treatment of these amides with organometallic reagents to complete the transformation. The success of such a tandem reaction relies on high *Z*-selectivity for the olefination reaction and retention of geometry in the second step. If the second process does not lead to a high degree of retention, efforts to gain high *Z*-selectivity in the first step would be useless. Thus, it would be very important to assess the ketone-forming step. For the *E*-counterparts, prevention of isomerization is not a critical issue, since they are highly favored. In fact, there are quite a few examples involving the transformation of aldehydes to *E*-α,β-unsaturated Weinreb amides[7] followed by further transformation to *E*-α,β-unsaturated aldehydes and ketones.[8] Herein, we report on the reaction of *Z*-α,β-unsaturated Weinreb amides with organo-lithium and -cerium reagents.



Since our primary objective was to determine the efficacy of the second step, efforts to obtain the *Z*-α,β-unsaturated Weinreb amides with high selectivity were carried out only briefly. Compared with the previously examined amide analog of Ando's ester reagent,[2] i.e., $(PhO)_2P(O)CH_2CON(Me)OMe$ (**1a**),[5] the sterically more demanding $(2\text{-}MeC_6H_4O)_2P(O)CH_2CON(Me)OMe$ (**1b**) was more effective for alkyl aldehydes, whereas the amide analog of Still's reagent,[1] i.e., $(CF_3CH_2O)_2P(O)CH_2CON(Me)OMe$ (**1c**),[9] was superior for aromatic aldehydes. Representative results are given in Table 1. Aliphatic aldehydes with higher steric demand tended to give lower selectivity.

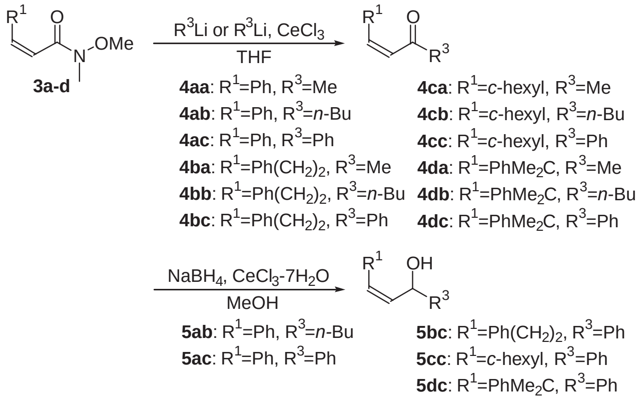
Table 1. HWE reaction with R^1CHO[a]

Entry	R^1	Reagent	Base	Product	*Z*:*E*[b]	Yield /%[c]
1[d]	Ph	**1a**	KHMDS	**3a**	72:28	67
2	Ph	**1b**	*n*-BuLi[e]	**3a**	88:12	71
3	Ph	**1c**	*t*-BuOK[f]	**3a**	97:3	88
4[d]	$Ph(CH_2)_2$	**1a**	NaH	**3b**	83:17	83
5	$Ph(CH_2)_2$	**1b**	NaH	**3b**	91:9	97
6	$Ph(CH_2)_2$	**1c**	KHMDS[f]	**3b**	85:15	87
7	*c*-Hexyl	**1b**	NaH[f]	**3c**	86:14	99
8	*c*-Hexyl	**1c**	*t*-BuOK[f,g]	**3c**	68:32	98
9	$PhMe_2C$	**1b**	NaH[f]	**3d**	84:16	58
10	$PhMe_2C$	**1c**	*t*-BuOK[f,g]	**3d**	43:57	35

[a]All of the reactions were run in THF at −78 °C. [b]Determined by the ¹H NMR (500 MHz) measurement of the crude mixture. [c]Combined isolated yield of *Z* and *E* olefins. The isomers of the products other than **3a** could be separated by chromatography, although with much difficulty in the case of **3d**. [d]From reference 5(c). [e]TMEDA was used as an additive. [f]18-Crown-6 was used as an additive. [g]The temperature was gradually raised to 0 °C.

The obtained α,β-Unsaturated Weinreb amides were not always separable by column chromatography, and thus were not necessarily separated upon examination with organometals. With organolithium reagents, MeLi, *n*-BuLi, and phenyllithium, the reactions were found to be rather messy as a whole and besides the desired α,β-unsaturated ketones arising from 1,2-addition, the crude reaction mixtures showed the presence of multiple saturated products in varying amounts, making purification somewhat tedious (Table 2).[10] The latter apparently formed by 1,4-addition or by secondary reactions to the 1,4-adducts. This is in contrast with *E*-α,β-unsaturated Weinreb amides, which reportedly undergo high yielding reactions.[7] However, the geometry of the olefin was found to be essentially intact during the reactions regardless of the identity of the substrate or organolithium reagent. The use of PhMgBr was found to lead to a high percentage of the *E*-olefin (Entry 7). The product ketones, especially those bearing a phenyl group, were prone to undergo some degree of isomerization.[11] Thus, in some cases, the product ketone was further reduced to the corresponding alcohol. This not only assured reaction selectivity (by reducing the possibility of adventituous isomerization) for isomerizable ketones, but also demonstrated that further transformations may be realized with minimal change in *E*–*Z* ratio.

With the intention of reducing the amount of the 1,4-addition products, the use of $CeCl_3$ as an additive was next examined (Table 3).[12,13]



4aa: R^1=Ph, R^3=Me
4ab: R^1=Ph, R^3=n-Bu
4ac: R^1=Ph, R^3=Ph
4ba: R^1=Ph(CH$_2$)$_2$, R^3=Me
4bb: R^1=Ph(CH$_2$)$_2$, R^3=n-Bu
4bc: R^1=Ph(CH$_2$)$_2$, R^3=Ph
4ca: R^1=c-hexyl, R^3=Me
4cb: R^1=c-hexyl, R^3=n-Bu
4cc: R^1=c-hexyl, R^3=Ph
4da: R^1=PhMe$_2$C, R^3=Me
4db: R^1=PhMe$_2$C, R^3=n-Bu
4dc: R^1=PhMe$_2$C, R^3=Ph

5ab: R^1=Ph, R^3=n-Bu
5ac: R^1=Ph, R^3=Ph
5bc: R^1=Ph(CH$_2$)$_2$, R^3=Ph
5cc: R^1=c-hexyl, R^3=Ph
5dc: R^1=PhMe$_2$C, R^3=Ph

Table 2. Reaction of unsaturated amides with RLi[a]

Entry	R^1	R^3	Product	Z:E[b]	(Z:E)[c]	$Z/(Z)$[d]	Yield /%[e]
1	Ph	Me	**4aa**	63:37	(69:31)	0.91	44
2	Ph	n-Bu	**4ab**	68:32	(69:31)	0.99	66
3[f]	Ph	Ph	**5ac**	97:3	(96:4)	1.00	70
4	Ph(CH$_2$)$_2$	Me	**4ba**	>99:1	(>99:1)	1.00	82
5	Ph(CH$_2$)$_2$	n-Bu	**4bb**	>99:1	(>99:1)	1.00	71
6[f]	Ph(CH$_2$)$_2$	Ph	**5bc**	>97:3	(97:3)	1.00	46
7[g,h]	Ph(CH$_2$)$_2$	Ph	**4bc**	70:30	(>99:1)	0.70	68

[a] All of the reactions were run in THF at −78 °C with 3 equiv. of RLi except where noted otherwise. The yields were not optimized. [b] Determined by the ^{1}H NMR (500 MHz) measurement of the crude mixtures. [c] The ratios of the unsaturated Weinreb amide substrates are in parentheses. [d] Z ratio of products divided by Z ratio of substrates. These values are rough indications of the degree of geometry retention. [e] Combined isolated yields of Z and E olefins. The isomers of the ketone products could be separated by chromatography, although somewhat less readily for **4aa** and **4ab**. [f] Further reduction was carried out on the crude ketone mixture. [g] The temperature was gradually raised to 0 °C. [h] PhMgBr (10 equiv.) was used.

Table 3. Reaction of unsaturated amides with RLi–CeCl$_3$[a]

Entry	R^1	R^3	Product	Z:E[b]	(Z:E)[c]	$Z/(Z)$[d]	Yield /%[e]
1	Ph	Me	**4aa**	67:33	(73:27)	0.92	77
2[f]	Ph	n-Bu	**5ab**	94:6	(94:6)	1.00	93
3[f]	Ph	Ph	**5ac**	94:6	(94:6)	1.00	93
4	Ph(CH$_2$)$_2$	Me	**4ba**	>99:1	(>99:1)	1.00	34(76)
5	Ph(CH$_2$)$_2$	n-Bu	**4bb**	>99:1	(>99:1)	1.00	95
6[f]	Ph(CH$_2$)$_2$	Ph	**5bc**	96:4	(97:3)	0.99	80
7	c-Hexyl	Me	**4ca**	95:5	(>99:1)	0.95	38(90)
8	c-Hexyl	n-Bu	**4cb**	96:4	(>99:1)	0.96	56(85)
9[f]	c-Hexyl	Ph	**5cc**	>99:1	(>99:1)	1.00	99
10	PhMe$_2$C	Me	**4da**	65:35	(71:29)	0.92	49(86)
11	PhMe$_2$C	n-Bu	**4db**	69:31	(71:29)	0.97	90
12[f]	PhMe$_2$C	Ph	**5dc**	96:4	(>99:1)	0.96	76

[a] Typical reactions were run in THF at −78 °C with 3 equiv. each of RLi and CeCl$_3$. [b–d] See footnotes of Table 2. [e] Combined isolated yields of Z and E olefins. Yields based on recovered starting material are in parentheses. The isomers of the ketone products could be separated by chromatography, although somewhat less readily for **4aa**. [f] Further reduction was carried out on the crude ketone mixture.

Besides those involving PhCeCl$_2$ where biphenyl formation was inevitable, the reactions were found to be rather clean ones, and other than the desired 1,2-product, practically only the unreacted starting material could be observed in the crude reaction mixtures. As for the geometry of the product ketones, compared with the organolithium reactions, there was a slight leakage in stereochemistry, but it was very minimal.

In summary, from a comprehensive point of view, we have found that organocerium reagents are very useful for the conversion of Z-α,β-unsaturated Weinreb amides to Z-α,β-unsaturated ketones. Efforts to increase selectivity in the olefination step for an efficient one-pot reaction, are currently in progress.

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