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Conjugate addition of organocopper reagents in dichloromethane to α,β-unsaturated esters

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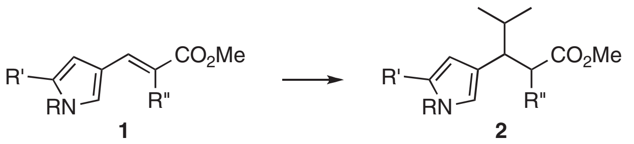
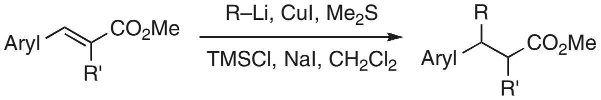
Abstract—Organocopper reagents in conjunction with Lewis acid activators provide greater stability than traditional cuprate reagents while maintaining the reactivity needed for conjugate addition reactions in dichloromethane. Whereas cuprates engage in cross-coupling pathways, organocopper nucleophiles are more selective for conjugate addition. The utility of organocopper reagents in dichloromethane for the conjugate addition to α,β-unsaturated esters is expanded upon herein.

In the course of studies directed toward the chemical synthesis of roseophilin,[1] we confronted the issue of a difficult conjugate addition of an isopropyl substituent to an α-alkyl-β-pyrrolyl-α,β-unsaturated ester (Eq. 1). Despite the wealth of information on organocuprate conjugate additions,[2] we could not find clear precedent to guide our investigation.



(1)

Our particular goal represents an extreme case in the scope of conjugate addition reactions[3] for at least two reasons: (a) pyrrolyl ester **1** is less electrophilic than typical enoates, due to conjugation with the electron-rich pyrrole; (b) isopropylcuprate is more hindered and less stable than other alkyl- or arylcuprate reagents.[4] Indeed, we have yet to satisfy our ambitions relating to the desired addition (Eq. 1), and we have taken recourse to alternative tactics.[5] Nonetheless, in the process of screening a wide range of reaction conditions and completing careful optimization of model conjugate addition reactions, we made relevant observations regarding the rather unconventional protocol of Nilsson and Olsson,[6,7] which features stable organo*copper* reagents solubilized in dichloromethane in conjunction with trimethylsilyl iodide (Eq. 2).[8] Previous reports mention ester enoates only briefly, but we found the Nilsson–Olsson protocol to have significant utility with respect to conjugate addition reactions of carbanionic nucleophiles to α,β-unsaturated esters (Table 1).



(2)

Entries 1–5 depict a series of addition reactions involving methyl cinnamate (**3**, Table 1).[9] One significant advantage of organocopper over cuprate species is that organocopper reagents are more robust, thereby permitting reactions to be conducted at higher temperatures and for prolonged times without decomposition. Such conditions are useful for addition of less stable carbanionic nucleophiles (entries 3 and 4), addition to less electrophilic alkenes (entries 6 and 7), and/or combinations thereof (entry 12). For example, to achieve the conjugate addition of *sec*-butylcopper (entry 4), the reaction mixture was stirred without external cooling for 3 h; analogous conditions for the conjugate addition of *sec*-butylcuprate have not been reported.[4]

The fidelity of mono-organocopper reagents for conjugate addition provides further advantages: conjugate addition to iodo-enoate **11** occurs more efficiently with phenylcopper than diphenylcuprate, which is more

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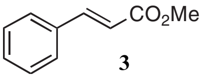
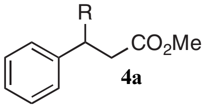
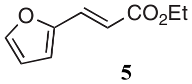
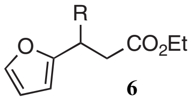
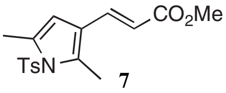
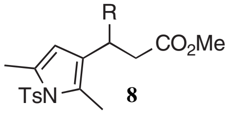
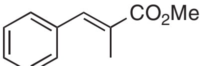
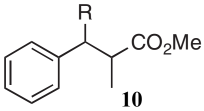
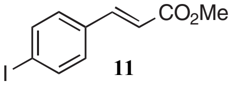
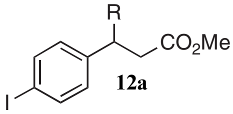
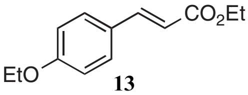
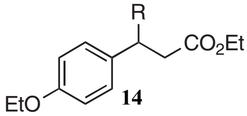
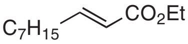
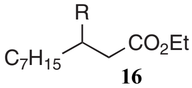
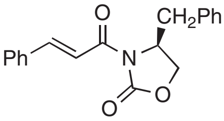
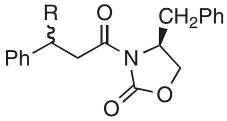
Table 1. Conjugate addition of organocopper reagents to α,β-unsaturated esters according to Eq. 2

Entry	α,β-Unsaturated ester	Conjugate addition product	R	Yield %[a]
1	 **3**	 **4a**	Me	95
2	**3**	**4b**	*n*-Bu	88
3	**3**	**4c**	*i*-Pr	74
4	**3**	**4d**	*s*-Bu	73
5	**3**	**4e**	Ph	>95
6	 **5**	 **6**	*i*-Pr	46
7	 **7**	 **8**	Ph	55
8	 **9**	 **10**	Ph	67[b]
9	 **11**	 **12a**	*i*-Pr	61
10	**11**	**12b**	Ph	94
11	**11**	**12b**	Ph	<64[c,d]
12	 **13**	 **14**	*i*-Pr	80
13	 **15**	 **16**	Ph	>95
14	 **17**	 **18**	Me	86[e]

[a] Isolated yield of material judged to be >95% pure by ^{1}H NMR analysis, unless otherwise indicated. See Supplementary data for details.

[b] Incomplete reaction; adjusted yield based on recovered starting material was 95%.

[c] Diphenylcuprate (2:1 Ph–Li: CuI) employed.

[d] Desired product recovered alongside unidentifiable impurities.

[e] Conjugate addition product **18** obtained in an approximately 1:1 ratio of diastereomers.

likely to engage in cross-coupling side reactions (entries 10 and 11, Table 1). Our efforts focused on β-aryl-enoates, although alkenoate substrates are suitable (entry 13 and Ref. 6). Diastereoselection in the addition of methylcopper to chiral cinnamic imide **17**[10] was negligible under the current conditions (entry 14).

Dichloromethane, along with dimethyl sulfide as a cosolvent, provides an excellent medium for these organocopper conjugate addition reactions. Aromatic hydrocarbons are less effective at solvating cuprate reagents, and Lewis-basic ethereal solvents are known to dampen the reactivity of cuprates,[11] likely through interactions with the metal centers.

In summary, observations on conjugate addition reactions to α,β-unsaturated carbonyl compounds are reported. Robust organocopper compounds withstand higher temperatures and longer reaction times than cuprate reagents, and organocopper reagents provide better selectivity for conjugate addition over competing cross-coupling pathways than that provided by cuprates. The mixture of trimethylsilyl chloride and sodium iodide promotes reactivity. This protocol and our observations are likely to be of use for other problems in chemical synthesis.

Acknowledgments

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Supplementary data

Experimental procedures, characterization data, and copies of NMR spectra are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.105.

References and notes

1. (a) Salamone, S. G.; Dudley, G. B. *Org. Lett.* **2005**, *7*, 4443–4445; For a review of the chemistry and biology of roseophilin and related compounds, see: (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582–3603.
2. (a) Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5560–5562; (b) *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; (c) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750–3771; (d) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 186–204; (e) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135–631; (f) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947–1038.
3. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergammon: Oxford, 1992.
4. Alkylcuprates, particularly secondary alkylcuprates, that possess β-hydrogens are susceptible to β-hydride elimination and other disproportionation pathways that are not available to aryl- or vinylcuprates.
5. Yang, J.; Katukojvala, S.; Dudley, G. B., unpublished results to be disclosed at a future date.
6. Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1988**, *44*, 2055–2062.
7. Related work: (a) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27–30; (b) Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1989**, *45*, 535–543; (c) Bergdahl, M.; Eriksson, M.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238–7244; (d) Eriksson, M.; Nilsson, M.; Olsson, T. *Synlett* **1994**, 271–272; (e) Bergdahl, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *Tetrahedron Lett.* **1995**, *36*, 3227–3230; (f) Eriksson, M.; Hjelmencrantz, A.; Nilsson, M.; Olsson, T. *Tetrahedron* **1995**, *51*, 12631–12644; (g) Eriksson, M.; Johansson, A.; Nilsson, M.; Olsson, T. *J. Am. Chem. Soc.* **1996**, *118*, 10904–10905.
8. Note that we used a combination of Me_3SiCl and NaI in lieu of Me_3SiI.
9. Active organocopper reagents were prepared at −78 °C by mixing 1.1 equiv of CuI, 2.0 equiv of NaI, and dimethyl sulfide (0.6 mL/mmol of CuI) in CH_2Cl_2 and then adding the appropriate organolithium reagent (1.0 equiv) and 2.0 equiv of Me_3SiCl. The active organocopper reagents were then typically employed in fivefold excess with respect to the unsaturated ester or imide, which was added as a solution in dry CH_2Cl_2 at −78 °C. The reaction mixtures were allowed to warm, typically to room temperature, and monitored for consumption of the activated alkene. Standard aqueous workup and purification techniques were employed to isolate the pure conjugate addition products. See Supplementary data for complete details and characterization data.
10. Dambacher, J.; Anness, R.; Pollock, P.; Bergdahl, M. *Tetrahedron* **2004**, *60*, 2097–2110.
11. (a) Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023–11024; (b) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128–3141.