Tetrahedron Letters 51 (2010) 1558–1561

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new Yb^{3+}-catalyzed pinacol and imine-coupling reaction

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ARTICLE INFO

Article history:
Received 18 November 2009
Revised 11 January 2010
Accepted 15 January 2010
Available online 22 January 2010

ABSTRACT

Ytterbium triflate, $Yb(OTf)_3$, catalyzes the intermolecular reductive homocouplings of imines, aldehydes, and ketones at loadings of 5 mol % in the presence of Mg and Me_3SiCl to give isolated yields of up to 95%. Diastereoselectivity of up to 4/96 (*dl*/*meso*) is achieved for aromatic aldehydes, up to 100% *dl* for aliphatic aldehydes, and 100% *dl* for an intramolecular imine coupling.

Samarium iodide (SmI_2) combines mild Lewis acidity with a useful reduction potential, and has proved to be a valuable and effective reagent for the reductive homocoupling of carbonyl[1] and imine[2] substrates to give the corresponding 1,2-diols or diamines. While it is a unique and extremely versatile reagent,[3] SmI_2 is rather expensive to buy and quite demanding to work with, making its use in stoichiometric quantities unattractive for large scale syntheses. In order to address these problems we have developed a SmI_2-catalyzed pinacol-coupling reaction that delivers high diastereoselectivity with a catalytic loading of 10 mol % using Mg as reductant.[4]

Annunziata et al. have reported the influence of various Lewis acids [including $Yb(OTf)_3$] used in conjunction with stoichiometric SmI_2 on the outcomes of pinacol[5] and imine-coupling reactions,[6,7] and have noted some enhancement of diastereoselectivity. This prompted us to investigate the use of catalytic SmI_2 with added Lewis acid and Mg as reductant.

Annunziata et al. reported one instance of catalytic SmI_2 (0.2 equiv) used in conjunction with Mg (8 equiv) and stoichiometric $Yb(OTf)_3$ for imine coupling, which gave an isolated yield of 62% and diastereoselectivity of 56/44 (*dl*/*meso*) for *N*-phenylbenzaldimine.[6] We started our work by re-examining this method applied to 4-chlorobenzaldehyde phenyl imine. We noted that the deep blue solution of SmI_2 was decolorized when it was added to anhydrous $Yb(OTf)_3$ and reasoned that SmI_2 was reducing Yb^{3+} to Yb^{2+}. This suggested to us that SmI_2 was not the active reducing agent and so we carried out a series of reactions in the absence of SmI_2 (Table 1). We also tested the activity of $Yb(OTf)_2$ (generated in situ by addition of EtMgBr to $Yb(OTf)_3$[8]) and found that it was completely inactive in the imine-coupling reaction. Mg in the absence of the rare earth Lewis acid was also inactive (Table 1, entry 1).

The use of stoichiometric $Yb(OTf)_3$ with Mg (entries 2 and 3) gave good isolated yields of coupled products, and we found that hydrated $Yb(OTf)_3$ was somewhat more active and gave slightly better diastereoselectivity. After this promising start we looked at sub-stoichiometric amounts of Lewis acid, and found that in the absence of Me_3SiX (X = Cl or OTf), the reaction was extremely sluggish. Anhydrous $YbCl_3$ (entry 9) is difficult to dissolve and was significantly less active than $Yb(OTf)_3$. The use of Me_3SiCl in the catalytic cycle will result in chloride-triflate exchange and the likely formation of $YbCl_3$, which might be detrimental to the reaction. In order to prevent this, we investigated the use of Me_3SiOTf with $Yb(OTf)_3$. However, this resulted in reduced catalytic activity (entry 8). We therefore conclude that the low activity of anhydrous $YbCl_3$ is due only to the difficulty of dissolving solid $YbCl_3$ in the solvents we used. We found that $Y(OTf)_3$ was also an effective catalyst for the imine-coupling reaction (Table 1, entry 9), though less active than $Yb(OTf)_3$, consistent with its lower Lewis acidity due to the larger ionic radius of Y^{3+} compared with Yb^{3+}. The activity of $Y(OTf)_3$, which does not have an accessible +2 oxidation state in solution, supports our view that the role of $Yb(OTf)_3$ is as a Lewis acid, and Yb is not involved as a reducing agent.

The scope of the imine-coupling reaction is shown in Table 2 where we explored substrates with a range of substituents and substitution patterns. Although the strongly electron-donating OMe substituent resulted in reduced activity, it was tolerated when it was present on just one of the aryl rings (entries 3, 4, 7 and 8), but not when it was present on both (entry 9). We had hoped to improve the diastereoselectivity by introducing an OMe substituent in a position where it could chelate to the Lewis acid catalyst (entries 3 and 4). In one case (entry 3 vs entry 1) there was a reversal in diastereoselectivity, but in the other case (entry 4 vs entry 2) the effect was negligible. It is noteworthy that halogen substituents were well tolerated (entries 2, 4, 5, and 6), and we observed no side reactions such as Grignard formation.

Both cyclic and acyclic polyether ligands are known to influence the redox chemistry of Sm and Yb by stabilizing the +2 oxidation

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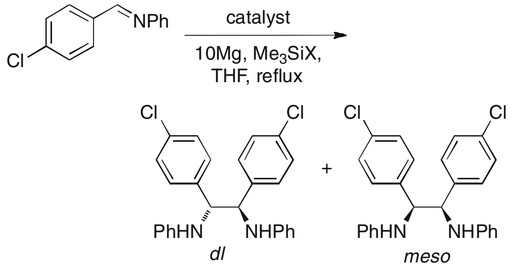
doi:10.1016/j.tetlet.2010.01.057

Table 1
Optimization of the conditions for imine coupling

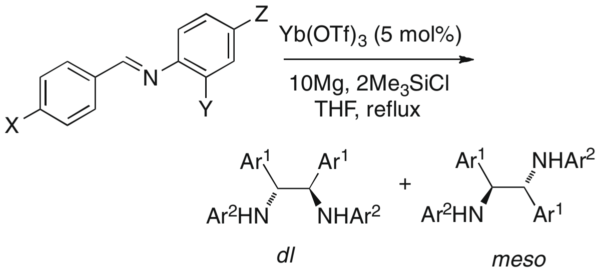


Entry	Catalyst/mol equiv	Mol equiv Me_3SiX	Time	Yield[a] (%), *dl:meso*[b]
1	None	1[e]	1.5 h	No reaction
2	$Yb(OTf)_3$[c]/1	0	1 h	81 (47:53)
3	$Yb(OTf)_3$[c]/1	0	7 h [d]	No reaction
4	$Yb(OTf)_3$[e]/1	0	40 min	81 (65:35)
5	$Yb(OTf)_3$[e]/0.5	0	3 d	69 (64:36)
6	$Yb(OTf)_3$[e]/0.5	1[f]	2 h	64 (63:37)
7	$Yb(OTf)_3$[e]/0.05	1[f]	45 min	77 (59:41)
8	$Yb(OTf)_3$[e]/0.05	1[g]	3 h	55 (48:52)
9	$YbCl_3$[c]/0.05	1[f]	4 h	61 (64:36)
10	$Y(OTf)_3$[e]/0.05	1[f]	1.25 h	70 (65:35)

[a] Isolated yield.
[b] Determined by ^1H NMR spectroscopy.
[c] Anhydrous.
[d] Reaction run at 40 °C.
[e] Hydrated.
[f] Me_3SiCl.
[g] Me_3SiOTf.

state.[9,10] We[4] and Skrydstrup and co-workers[11] have shown that the addition of tetraglyme enhances the diastereoselectivity of SmI_2-catalyzed pinacol coupling, and so we investigated the effect of added ligand (1:1 ligand:catalyst) on the outcome of the imine-coupling reactions reported here. We found that added ligand (2,2-bipyridyl, triethyleneglycol, triglyme, tetraglyme, 18-crown-6 or 15-crown-5) had no significant effect on either the yield or diastereoselectivity.

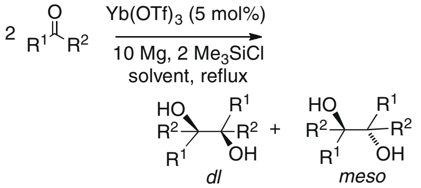
Table 2
$Yb(OTf)_3$-catalyzed imine coupling

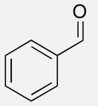
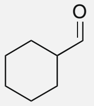
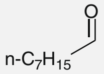
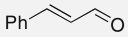
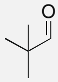
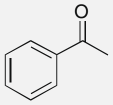


Entry	X	Y	Z	Time	Yield[a] (%), *dl:meso*[b]
1	H	H	H	2 h	77 (62:38)
2	Cl	H	H	45 min	77 (59:41)
3	H	OMe	H	4 h	63 (31:69)
4	Cl	OMe	H	3.5 h	50 (65:35)
5	H	H	Br	2.5 h	69 (40:60)
6	Cl	H	Br	2 h	79 (50:50)
7	OMe	H	H	5 h	63 (67:33)
8	H	H	OMe	5 h	56 (56:44)
9	OMe	H	OMe	18 h	No product isolated

[a] Isolated yield.
[b] Determined by ^1H NMR spectroscopy.

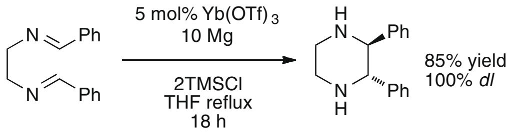
Table 3
$Yb(OTf)_3$-catalyzed pinacol coupling of aldehydes and ketones



Entry	Substrate	Solvent[a]	Time	Yield[b] (%), *dl:meso*[c]
1a		THF	90 min	91 (80:20)
1b		CH_2Cl_2/THF	3 h	71 (4:96)
1c		CH_2Cl_2/THF[d]	4 h	74 (27:63)
1d		MeCN	45 min	95 (40:60)
2a		THF	20 h	64 (75:25)
2b		CH_2Cl_2/THF	24 h	65 (93:7)
2c		CH_2Cl_2/THF[d]	30 h	60 (60:40)
2d		MeCN	23 h	69 (60:40)
3a		THF	15 h	61 (69:31)
3b		CH_2Cl_2/THF	15 h	60 (60:40)
4a		THF	3.5 h	55 (56:44)
4b		CH_2Cl_2/THF	3.5 h	53 (79:21)
5a		THF	18 h	95 (*dl* only)
5b		CH_2Cl_2/THF	18 h	89 (*dl* only)
6a		THF	90 min	85 (67:33)
6b		CH_2Cl_2/THF	3 h	75 (55:45)

[a] CH_2Cl_2/THF = 4:1.
[b] Isolated yield.
[c] Determined by GC and confirmed by GCMS.
[d] Reaction run at room temperature.

Intramolecular imine coupling is a useful route to 2,3-disubstituted piperazines, and this reaction has been reported using Mn as reductant with a Brønsted acid catalyst,[12] and using Zn as reductant catalyzed by a stoichiometric amount of the Lewis acid $[TiCl_2(OPr^i)_2]$.[13] When we applied our imine-coupling protocol to this reaction we achieved a yield of 85% after recrystallization and 100% diastereoselectivity for the *dl* product, making this an attractive alternative to the published methods.



After these promising results with imine coupling, we next investigated $Yb(OTf)_3$ catalysis of the pinacol-coupling reaction (Table 3). Isolated yields were good to excellent and significantly, we observed no reduction product in any of these reactions.

In our previous work with SmI_2/tetraglyme-catalyzed pinacol coupling we found a clear selectivity for the *meso* product with aromatic substrates and the *dl* product with aliphatic substrates.[4] The stereochemical outcome of the present method is much less clear-cut, and in the three solvent systems that we investigated, we observed some dramatic effects on the diastereoselectivity.

In THF the *dl* product was favored in all cases (aromatic and aliphatic) that we examined. THF is likely to compete with the substrate for binding to the Lewis acid center, possibly reducing catalytic activity. We therefore examined the 4:1 CH_2Cl_2/THF solvent system and found that although it resulted in slightly decreased rather than enhanced activity, in some cases it had a dramatic effect on the diastereoselectivity of the reaction. For benzaldehyde (Table 3, entries 1a and b) the diastereoselectivity was reversed on changing solvent, and in CH_2Cl_2/THF the *meso* product was heavily favored. For cyclohexanecarboxaldehyde, (Table 3, entries 2a and b) the use of CH_2Cl_2/THF dramatically enhanced the selectivity toward the *dl* isomer. An enhancement of diastereoselectivity in CH_2Cl_2/THF was also observed for the unsaturated substrate cinnamaldehyde (Table 3 entries 4a and b). We observed slightly enhanced activity in MeCN cf. THF for the coupling of benzaldehyde (Table 3, entry 1c) and cyclohexanecarboxaldehyde (entry 2c), but poorer diastereoselectivity. As our reactions were carried out in refluxing solvents, variation of the solvent resulted not only in different donor properties and dielectric constants, but also in a change in reaction temperature. The highest diastereoselectivity was achieved in the lowest boiling solvent, CH_2Cl_2/THF (entries 1b and 2b), and so we repeated these reactions at room temperature (entries 1c and 2c), and found that the reduced reaction temperature gave significantly poorer diastereoselectivity. This proves that the high diastereoselectivity achieved in CH_2Cl_2/THF is due to the properties of the solvent system and is not simply due to reaction temperature.

We found that tetraglyme was highly effective in enhancing the diastereoselectivity of SmI_2-catalyzed pinacol-coupling reactions[4] and so we examined the effect of this pentadentate ligand on the pinacol coupling of benzaldehyde; the results are summarized in Table 4. In the three solvent systems that we examined there was a slight decrease in activity in the presence of tetraglyme, but there was a dramatic effect on diastereoselectivity, in all cases resulting in selectivity for the *meso* diastereomer. In THF (entries 1a and b) addition of tetraglyme caused reversal of diastereoselectivity; in MeCN, an increase in selectivity was observed, and in CH_2Cl_2/THF there was a slight decrease in selectivity.

Two paths for the pinacol-coupling reaction can be envisaged, as summarized in Scheme 1. Path I, an intermolecular coupling, results in *meso* product and is favored when there is a high concentration of ketyl radical. This situation is most likely with an easily reduced substrate, a more powerful Lewis acid or a higher reaction temperature. Path II is an intramolecular coupling, and two factors are required for this path to predominate: there must be a low concentration of ketyl radical and sufficient coordinative unsaturation at the Lewis acid to allow coordination of a second substrate molecule. Solvent effects in this reaction are complex; the relevant factors are: dielectric constant (which will influence Lewis acid strength), boiling point (which determines the reaction temperature), and donor number (which will determine the competition between solvent and substrate for coordination to the Lewis acid). Given the complexity of the reaction variables it is not surprising that the diastereoselectivity appears unpredictable.

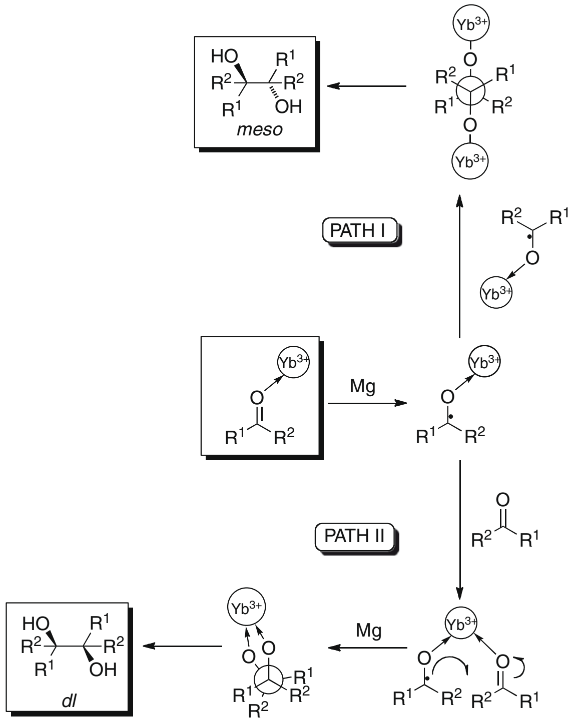
The coupling of benzaldehyde (Table 4) is the simplest case to consider. The most rapid reaction was achieved in acetonitrile (entry 2a), which has the highest boiling point (82 °C) and the highest dielectric constant (37), and in the absence of tetraglyme there was a slight selectivity for the *meso* diastereomer, consistent with predominance of Path I. Addition of tetraglyme would limit the available binding sites at the Lewis acid, effectively blocking Path II, and so addition of tetraglyme resulted in excellent *meso* selectivity (entry 2b). In THF (bp 66 °C; dielectric constant 7.5), the Lewis acidity of $Yb(OTf)_3$ is reduced compared with that in MeCN and this, combined with the somewhat reduced reaction temperature, is expected to give a lower concentration of coordinated ketyl radicals and hence lead to predominance of Path II and *dl* selectivity (entry 1a). Added tetraglyme would occupy five coordination sites at Yb^{3+},[14] blocking Path II and resulting in *meso* selectivity (entry 1b). The situation was much more finely balanced in CH_2Cl_2, where the reaction was significantly slower and addition of tetraglyme resulted in some reduction in *meso* selectivity (entries 3a and 3b).

In conclusion, we have developed an extremely straightforward method for the intermolecular homocoupling of aryl imines and aromatic and aliphatic carbonyl compounds, using Mg as the reducing agent and $Yb(OTf)_3$ as a Lewis acid catalyst.[15] Products are isolated in good to excellent yields and diastereoselectivity of up to 100% has been achieved.

Table 4
Effect of solvent and added ligand on the pinacol coupling of benzaldehyde[a]

Entry	Solvent	Ligand	Time	Yield[b] (%), *dl:meso*[c]
1a	THF	None	1.5 h	91 (80:20)
1b		Tetraglyme	1.5 h	80 (6:94)
2a	MeCN	None	45 min	95 (40:60)
2b		Tetraglyme	45 min	62 (5:95)
3a	CH_2Cl_2/THF[d]	None	3 h	71 (4:96)
3b		Tetraglyme	4 h	69 (13:87)

[a] Conditions: 0.05 equiv hydrated $Yb(OTf)_3$, 1 equiv Me_3SiCl, 10 equiv Mg, reflux.
[b] Isolated yield.
[c] Determined by GC and confirmed by GC–MS.
[d] CH_2Cl_2/THF = 4:1.



Scheme 1. Diastereoselectivity in the $Yb(OTf)_3$-catalyzed pinacol-coupling reaction.

Supplementary data

Characterization data for key compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.057.

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14. Aspinall, H. C.; Dwyer, J. L. M.; Greeves, N.; McIver, E. G.; Woolley, J. C. *Organometallics* **1998**, *17*, 1884–1888.
15. *Experimental procedures. General procedure for Yb(OTf)$_3$-catalyzed imine coupling*: Yb(OTf)$_3$ (0.05 mmol), imine (1 mmol) and activated Mg turnings (10 mmol) were placed in Schlenk flask and freshly distilled THF (8 cm^3) was added. The mixture was stirred for 10 min and then Me$_3$SiCl (0.2 cm^3, 1 mmol) was added and the mixture was heated to reflux with stirring under an atmosphere of Ar or N$_2$. The reaction was monitored by TLC and was quenched with brine (20 cm^3). The crude product was extracted with EtOAc (3 × 20 cm^3) and the combined extracts were dried (MgSO$_4$). The crude product was purified by flash chromatography using hexane/Et$_2$O on silica.
    General procedure for Yb(OTf)$_3$-catalyzed pinacol-coupling reaction: Yb(OTf)$_3$ (0.05 mmol) and activated Mg powder (10 mmol) were placed in a Schlenk flask and freshly distilled THF (8 cm^3) was added. Aldehyde or ketone (1 mmol) was added and the mixture was stirred for 10 min. Me$_3$SiCl (0.2 cm^3, 1 mmol) was then added and the mixture was heated to reflux with stirring under an atmosphere of Ar or N$_2$. The reaction was monitored by TLC and was quenched with saturated brine (20 cm^3). The crude product was extracted with EtOAc (3 × 20 cm^3) and the combined extracts were dried (MgSO$_4$). The crude product was purified by flash chromatography using hexane/Et$_2$O on silica.
    General procedure for imine synthesis: The aldehyde (10 mmol), aniline (10 mmol) and 4 Å molecular sieves (1.66 mm pellets, 10 g) were mixed in dry CH$_2$Cl$_2$ (30 cm^3). The mixture was allowed to stir at rt and reaction was monitored by TLC. When the reaction was complete, the mixture was filtered through a pad of Celite and the residue was washed with dry CH$_2$Cl$_2$. The filtrate was collected and evaporated in vacuo and the imine was then dried under high vacuum and stored in a sealed container at rt.